FORMULATION AND EVALUATION OF ETODOLAC IMMEDIATE RELEASE TABLETS BY USING SUPERDISINTEGRANTS AND ITS STABILITY STUDIES

Dissertation work submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI

In partial fulfillment of the award of degree of

MASTER OF PHARMACY (PHARMACEUTICS)

MARCH 2009

College of Pharmacy

SRI RAMAKRISHNA INSTITUTE OF PARAMEDICAL SCIENCES

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Submitted by

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Under the guidance of

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Vice Principal
Head, Department of Pharmaceutics

March 2009

College of Pharmacy

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CERTIFICATE

This is to certify that the dissertation entitled ***"FORMULATION AND EVALUATION OF ETODOLAC IMMEDIATE RELEASE TABLETS BY USING SUPERDISINTEGRANTS AND ITS STABILITY STUDIES"*** *was carried out by* **Ms. SHAIK RIHANA PARVEEN,** *in the Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, which is affiliated to The Tamilnadu Dr. M.G.R. Medical University, Chennai, under the direct supervision and guidance of* **Dr. M. Gopal Rao, M.Pharm., Ph.D.,** *Department of Pharmaceutics, College of Pharmacy, SRIPMS, Coimbatore.*

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Shaik. Rihana Parveen

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ABBREVIATIONS

ICH	-	International conference on harmonization
USP	-	United States pharmacopoeia
BP	-	British pharmacopoeia
JP	-	Japanese pharmacopoeia
Ph Eur	-	European pharmacopoeia
IP	-	Indian pharmacopoeia
NF	-	National formulary
IR	-	Immediate release
API	-	Active pharmaceutical ingredient
PVP	-	Polyvinyl pyrrolidine
MCC	-	Micro crystalline cellulose
LMH	-	Lactose monohydrate
CMC	-	Carboxy methyl cellulose
TLC	-	Thin layer chromatography
Min	-	Minutes
Hrs	-	Hours
b.i.d.	-	Two times a day
t.i.d.	-	Three times a day
Eto	-	Etodolac

PURPOSE OF WORK AND PLAN OF WORK

PURPOSE OF WORK

- Etodolac, is a nonsteroidal anti-inflammatory drug (NSAIDs), used in the treatment of arthritis and the alleviation of pain[1].
- Etodolac is rapidly absorbed after oral administration.
- The onset of action is 30 minutes and C_{max} achieved within 1-2 hours of administration of tablets or capsules.
- The bioavailability of Etodolac from tablets and capsules is 100% relative to oral solution.
- Pharmacokinetics of Etodolac exhibit dose proportionality over the 100-300 mg dose range for immediate release formulation[2].
- Fast track cardiac anesthesia requires lower dose of opioids in the peri and postoperative period.
- The oral use of Etodolac with rectal buprenorphine reduces postoperative pain scores immediately after fast track cardiac surgery.
- The faster the release of Etodolac from the dosage form is better for the management of pain in postoperative cardiac surgery cases[3].
- Etodolac is safe over other NSAIDs and it has less ulcerogenic activity[4].
- As Etodolac immediate release 300 mg tablets formulation is not available globally, the present study is attempted to prepare immediate release tablets of Etodolac.

- By using superdisintegrants such as polyplasdone XL-10 (crospovidone) and sodium starch glycolate were added in three different methods:
  - Intragranular (before granulation)
  - Extra granular (after granulation) and
  - Partly Intra and Extragranular method of addition
- And these superdisintegrants were added in three different ratios' (2%, 4%, and 6%) to develop a stable immediate release formulation by wet granulation method. So as to increase the rate of drug release from the dosage form to increase the dissolution rate.

PLAN OF WORK

- ✓ Literature survey on Etodolac drug and immediate release dosage forms.
- ✓ Preformulation studies.
- ✓ Formulation of Etodolac immediate release tablets by intragranular, extragranular, and partly intra and extragranular method of addition, by using superdisintegrants such as (polyplasdone XL-10) crospovidone and sodium starch glycolate at three different ratios (2%, 4%, and 6%).
- ✓ Evaluation tests.
- ✓ Stability studies.

INTRODUCTION

THE HISTORICAL BACKGROUND OF IMMEDIATE RELEASE TABLETS

Since man first began to treat illness using oral administration of herbs and other available materials, there have been a problem of how to take the medicines because many drugs, whether natural or synthetic, are bitter. Many of early developments in formulations were designed with taste masking and convenience in mind. We formulate to convert bulk drugs into medicines that the patient can use. In case of oral administration, both tablets and capsules are convenient for patients as they allow self-medication and can be easily designed to mask any unpleasant taste. Besides tablets and capsules, there are powders, usually taken dispersed in water. But tablets and capsules are comparatively recent developments. In the past drugs were formulated as powders, cachets (made of rice starch), and pillules (pills). Tablets and capsules are used because, in many respects, they are easier and can be manufactured at high speed on today's modern equipment.

Tablets can be designed for use as immediate release products or by suitable modification of the composition and manufacturing process, can also be designed as modified release products, with many different potential release patterns.

However, for immediate release tablets, tablet disintegrants play an important role in ensuring that the tablet matrix break up on contact with the fluid in the stomach to allow the release of the active drug which then become available, in whole or in part, for absorption from the gastrointestinal tract (GIT). Although most drugs are absorbed from the GIT after passing through the stomach, it is nevertheless important with immediate release products that the tablet disintegrates properly in the

stomach to release the drug and allow it to be absorbed quickly after passing through the pyloric sphincter and on into duodenum and beyond[5].

IMMEDIATE RELEASE TABLETS

Definition

Tablet may be defined as the solid unit dosage form of medicament with or without suitable diluents and prepared either by molding or by compression. In "pharmaceutical chemist" terminology

A tablet is a combination of ingredients that is compressed into a solid mass. The basic components of an immediate release pharmaceutical tablet are active drug substances and other excipients.

ADVANTAGES OF TABLETS

- Tablets are unit dosage forms that provide an accurate, stable dose with greatest precision and least content variability.
- Tablets are easy to use, handle and carry by the patient.
- Tablets are attractive and elegant in appearance.
- Tablets are the most stable dosage form with respect to their physical, chemical and microbiological attributes.
- The manufacturing cost of tablets is low as compared to other dosage form and their manufacturing speed is also quite high.
- The packaging and shipping of tablets is comparatively easy and cheap.
- The unpleasant taste and odor of medicament(s) can be easily masked by sugar-coating.
- The incompatibilities of medicament(s) and their deterioration due to environmental factors are less in case of tablet.
- Whenever a fractional dose is required, tablets are divided into halves and quarters by drawing lines during manufacturing to facilitate breakage.

- ❖ They are more suitable for large scale production than other oral dosage forms.
- ❖ Tablets provide administration of even minute dose of drug in an accurate amount.
- ❖ Their identification is probably the easiest because of variety of shapes and colors.
- ❖ Tablets are formulated with certain special release profile products such as enteric or delayed release products.
- ❖ They are economical as their cost is lowest as compared to other oral dosage forms.

DISADVANTAGES OF TABLETS

- ▪ Drugs that are amorphous in nature or have low density character are difficult to compress into tablet.
- ▪ Hygroscopic drugs are not suitable candidate for compressed tablets.
- ▪ Drugs having poor wetting properties, slow dissolution profile and high optimal gastro intestinal absorption are difficult or impossible to formulate as a tablet.
- ▪ Drugs having bitter taste and objectionable odor requires special treatment like coating or encapsulation which may increase their production cost.
- ▪ Some drugs which preferably get absorbed from the upper part of GIT may cause bioavailability problem in tablet dosage form.
- ▪ Swallowing of tablets especially by children and critically ill patients is very difficult.

TYPES AND CLASSES OF TABLETS[6]

TABLE NO. 1: TYPES AND CLASSES OF TABLETS

Oral Tablets for ingestion
✓ Compressed Tablets or Standard Compressed Tablets.
✓ Multiple Compressed Tablets (MCT).
✓ Layered Tablets.
✓ Compression – Coated Tablets.
✓ Repeated – Action Tablets.
✓ Delayed – Action and Enteric Coated Tablets.
✓ Sugar- and Chocolate- Coated Tablets.
✓ Film- Coated Tablets.
✓ Chewable Tablets
Tablets Used in the Oral Cavity
✓ Sublingual Tablets.
✓ Buccal Tablets.
✓ Troches and Lozenges.
✓ Dental cones.
Tablets Administered by Other Routes
✓ Implantation Tablets.
✓ Vaginal Tablets.
Tablets Used to Prepare Solutions
✓ Effervescent Tablets.
✓ Dispensing Tablets (DT).
✓ Hypodermic Tablets (HT).
✓ Tablet Triturates (TT).

VARIOUS EXCIPIENTS USED IN TABLET FORMULATION AND THEIR FUNCTIONALITIES

Excipient means any component other than the active pharmaceutical ingredient(s) intentionally added to the formulation of a dosage form. Excipients play a crucial role in design of the delivery system, determining its quality and performance.

TABLE NO. 2: EXCIPIENTS AND THEIR FUNCTIONALITIES

EXCIPIENT	FUNCTION
Diluents or Fillers E.g.: Lactose, Mannitol, Sorbitol, Dextrose, etc.	Diluents make the required bulk of the tablet when the drug dosage itself is inadequate to produce tablets of adequate weight and size.
Binders or Granulating agents or Adhesives E.g.: Acacia, gelatin, Polyvinylpyrrolidone, etc.	Binders are added to tablet formulations to add cohesiveness to powders, thus providing the necessary bonding to form granules, which under compaction form a cohesive mass or a compact which is referred to as a tablet.
Disintegrants E.g.: Starch, Clays, Cellulose, etc.	A disintegrant is added to most tablet formulations to facilitate a breakup or disintegration of the tablet when placed in an aqueous environment.
Antifrictional Agents	
Lubricants E.g.: Talc, Calcium and magnesium stearate, etc.	Lubricants are intended to reduce the friction during tablet formation in a die and also during ejection from die cavity.
Anti-adherents E.g.: colloidal silica	Anti-adherents are added to reduce sticking or adhesion of any of the tablet granulation or powder to the faces of the punches or to the die wall.

EXCIPIENT	FUNCTION
Glidants E.g.: Silica derivatives - colloidal silicon, corn starch, etc.	Glidants are intended to promote the flow of tablet granulation or powder mixture from hopper to the die cavity by reducing friction between the particles.
MISCELLANEOUS	
Wetting agents / Solubilizers E.g.: Polysorbate 80.	Wetting agents are added to tablet formulation to aid water uptake during disintegration and assist drug dissolution.
Dissolution retardants E.g.: Waxes – bees wax.	Dissolution retardants as the name suggest, retards the dissolution of active pharmaceutical ingredient(s)
Dissolution enhancers E.g.: Surfactant and solubilizers.	Dissolution enhancers as the name suggest, enhance the dissolution rate of active pharmaceutical ingredient(s).
Adsorbents	Adsorbents are capable of retaining large quantities of liquids without becoming wet; this property of absorbent allows many oils, fluid extracts and eutectic melts to be incorporated into tablets.
Buffers E.g.: Sodium hydroxide	Buffers are added to provide suitable micro environmental pH to get improved stability and / or bioavailability.
Antioxidants E.g.: Ascorbic acid, sodium sulfite, sodium bisulfite, butylated hydroxyl toluene, etc.	Antioxidants are added to maintain product stability, they act by being preferentially oxidized and gradually consumed over shelf life of the product.
Chelating agents E.g.: Di sodium edentate,	Chelating agents are added to protect against autoxidation; they act by forming complexes with the heavy metal ions which are often required to initiate oxidative reactions.

EXCIPIENT	FUNCTION
Preservatives E.g.: Benzyl alcohol, methyl paraben, propyl paraben, etc.	Preservatives are added to tablet formulation in order to prevent the growth of micro-organisms.
Colours E.g.: Food Drug and Cosmetic, Drug and Cosmetic dyes	Colours are added to tablet formulation for following purposes: to disguise off colour drugs, product identification and for production of more elegant product.
Flavours E.g.: Peppermint oil	Flavours are added to tablet formulation in order to make them palatable enough in case of chewable tablet by improving the taste.
Sweeteners E.g.: Saccharin	Sweeteners are added to tablet formulation to improve the taste of chewable tablets.

METHOD OF TABLET PREPARATION

There are three general methods of tablet preparation.

- ❖ Direct compression method
- ❖ Dry granulation method
- ❖ Wet granulation method

GRANULATION

Granulation may be defined as a size enlargement process which converts small particles into physically stronger and larger agglomerates.

IDEAL CHARACTERISTICS OF GRANULES

The ideal characteristics of granules include spherical shape, smaller particle size distribution with sufficient fines to fill void spaces between granules, adequate moisture (between 1-2%), good flow, good compressibility and sufficient hardness. The effectiveness of granulation depends on the following properties

- Particle size of the drug and excipients.
- Type of binder (strong or weak).
- Volume of binder (less or more).
- Wet massing time (less or more).
- Amount of shear applied.
- Drying rate (Hydrate formation and polymorphism)

WET GRANULATION

The most widely used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing and drying.

IMPORTANT STEPS INVOLVED IN THE WET GRANULATION

- ✓ Mixing of the drug(s) and excipients.
- ✓ Preparation of binder solution.
- ✓ Mixing of binder solution with powder mixture to form wet mass screens.
- ✓ Coarse screening of wet mass using a suitable sieve (6-12).
- ✓ Drying of moist granules.
- ✓ Screening of dry granules through a suitable sieve (14-20).
- ✓ Mixing of screened granules with disintegrant, glidant, and lubricant.

LIMITATION OF WET GRANULATION

- The greatest disadvantage of wet granulation is its cost. It is an expensive process because of labor, time, equipment, energy and space requirements.
- Loss of material during various stages of processing.
- Stability may be major concern for moisture sensitive or thermo labile drugs.

- Multiple processing steps add complexity and make validation and control difficult.
- An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated.

SPECIAL WET GRANULATION TECHNIQUES

- High shear mixture granulation.
- Fluid bed granulation.
- Extrusion-spheronization.
- Spray drying.

DISINTEGRATION

Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The drugs solubility mainly depends on physical – chemical characteristics of the drug. However, the rate of drug dissolution is greatly influenced by disintegration of the tablet. The drug will dissolve at a slower rate from a non-disintegrating tablet due to exposure of limited surface area to the fluid. The disintegration test is an official test and hence a batch of tablet must meet the stated requirements of disintegration.

Disintegrants, are important excipient of the tablet formulation, are always added to tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants. The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet.

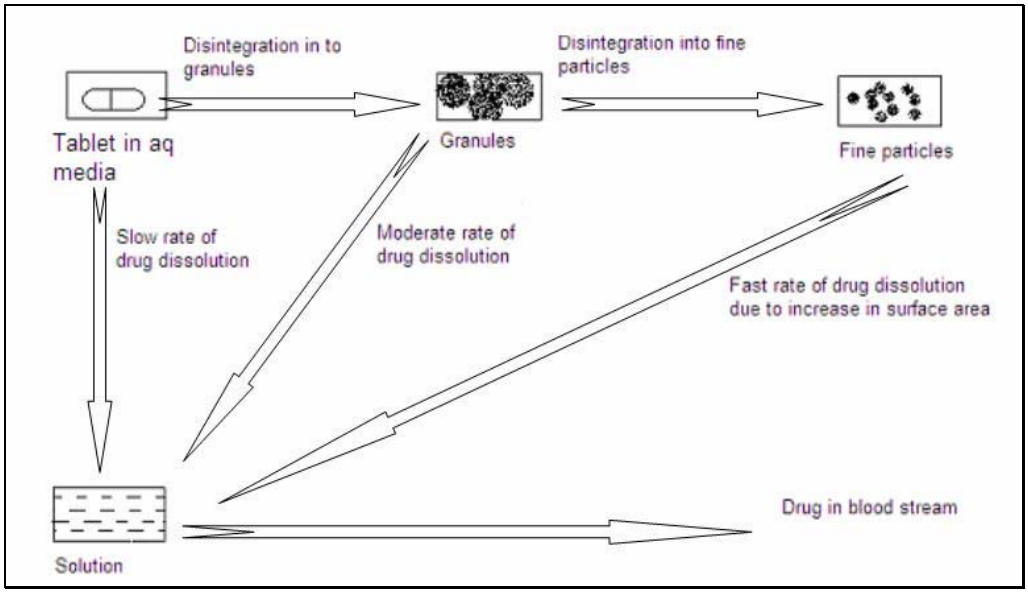


FIGURE NO. 1: TABLET DISINTEGRATION AND SUBSEQUENT DRUG DISSOLUTION

MECHANISM OF TABLET DISINTEGRANTS

The tablet breaks to primary particles by one or more of the mechanisms listed below:

- By capillary action.
- By swelling.
- Because of heat of wetting.
- Due to disintegrating particle/particle repulsive forces.
- Due to deformation.
- Due to release of gases.
- By enzymatic action.

BY CAPILLARY ACTION

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens

the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tabletting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

BY SWELLING

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

BECAUSE OF HEAT OF WETTING (AIR EXPANSION)

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and can not describe the action of most modern disintegrating agents.

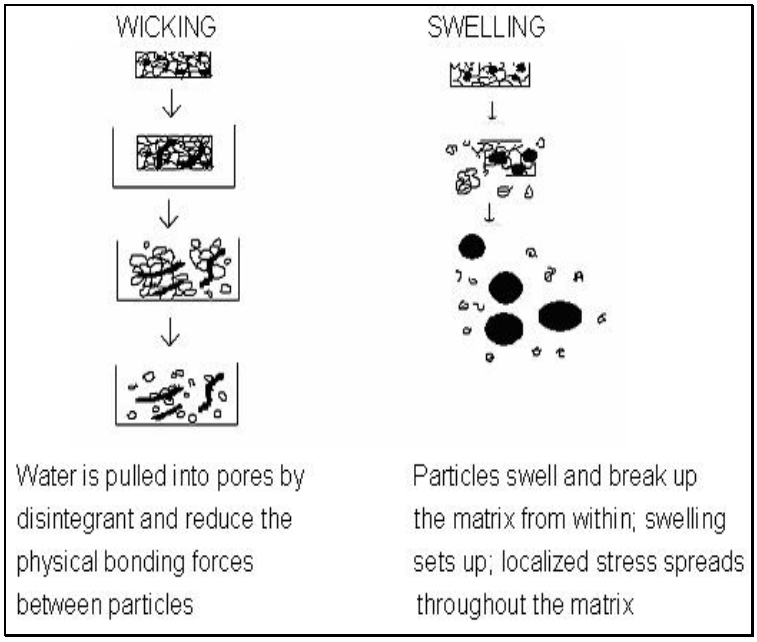


FIGURE NO. 2: MECHANISM OF WICKING AND SWELLING

DUE TO DISINTEGRATING PARTICLE/PARTICLE REPULSIVE FORCES

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non-swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

DUE TO DEFORMATION

Hess had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of

the deformed particles produces a break up of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

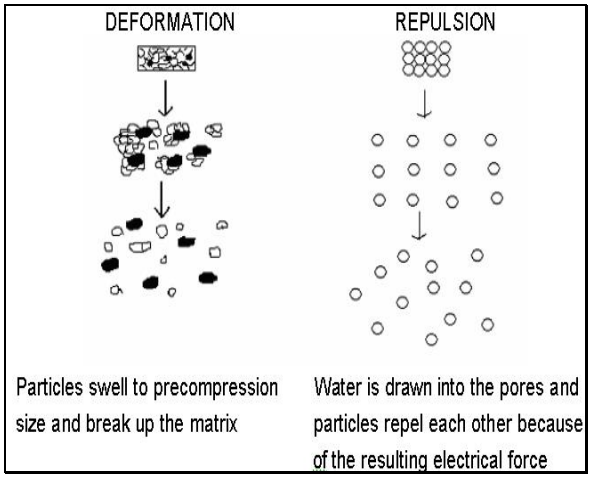


FIGURE NO. 3: MECHANISM OF DEFORMATION AND REPULSION

DUE TO RELEASE OF GASES

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

BY ENZYMATIC REACTION

Here, enzymes presents in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration.

DISINTEGRATING ENZYMES

TABLE NO. 3: DISINTEGRATING ENZYMES

ENZYMES	BINDER
Amylase	Starch
Protease	Gelatin
Cellulose	Cellulose and its derivatives
Invertase	Sucrose

METHODS OF ADDITION OF DISINTEGRANTS

The method of addition of disintegrants is also a crucial part. Disintegrating agent can be added either prior to granulation (intragranular) or prior to compression (after granulation i.e. extragranular) or at the both processing steps. Extragranular fraction of disintegrant (usually, 50% of total disintegrant requires) facilitates breakup of tablets to granules and the intragranular addition of disintegrants produces further erosion of the granules to fine particles.

TYPES OF DISINTEGRANTS

STARCH

Starch was the first disintegrating agent widely used in tablet manufacturing. Before 1906 potato starch and corn starch were used as disintegrants in tablet formulation. The mechanism of action of starch is wicking and restoration of deformed starch particles on contact with aqueous fluid and in doing so release of certain amount of stress which is responsible for disruption of hydrogen bonding formed during compression

PREGELATINIZED STARCH

Pregelatinized starch is produced by the hydrolyzing and rupturing of the starch grain. It is a directly compressible disintegrants and its

optimum concentration is 5-10%. The main mechanism of action of Pregelatinized starch is through swelling.

MODIFIED STARCH

To have a high swelling properties and faster disintegration, starch is modified by carboxy methylation followed by cross linking, which is available in market as cross linked starch. One of them is sodium starch glycolate. Even low substituted and Primogel, carboxymethyl starches are also marketed as Explotab. Mechanism of action of this modified starches are rapid and extensive swelling with minimum gelling. And its optimum concentration is 4-6 %. If it goes beyond its limit, then it produces viscous and gelatinous mass which increases the disintegration time by resisting the breakup of tablet. They are highly efficient at low concentration because of their greater swelling capacity.

CELLULOSE AND ITS DERIVATIVES

Sodium carboxy methylcellulose (NaCMC and Carmelose sodium) has highly hydrophilic structure and is soluble in water. But when it is modified by internally crosslinking we get modified crosslinked cellulose i.e. Croscarmelose sodium which is nearly water insoluble due to cross linking. It rapidly swells to 4-8 times its original volume when it comes in contact with water.

MICROCRYSTALLINE CELLULOSE (MCC)

MCC exhibit very good disintegrating properties because MCC is insoluble and act by wicking action. The moisture breaks the hydrogen bonding between adjacent bundles of MCC. It also serves as an excellent binder and has a tendency to develop static charges in the presence of excessive moisture content. Therefore, sometimes it causes separation in

granulation. This can be partially overcome by drying the cellulose to remove the moisture.

ION-EXCHANGE RESIN

Ion exchange resin (Ambrelite IPR-88) has highest water uptake capacity than other disintegrating agents like starch and Sodium CMC. It has tendency to adsorb certain drugs.

ALGINATES

Alginates are hydrophilic colloidal substances which has high sorption capacity. Chemically, they are alginic acid and salts of alginic acid. Alginic acid is insoluble in water, slightly acidic in reaction. Hence, it should be used in only acidic or neutral granulation. Unlike starch and MCC, alginates do not retard flow and can be successfully used with ascorbic acid, multivitamin formulations and acid salts of organic bases.

MISCELLANEOUS

This miscellaneous category includes disintegrants like surfactants, gas producing disintegrants and hydrous aluminium silicate. Gas producing disintegrating agents is used in soluble tablet, dispersible tablet and effervescent tablet.

TABLE NO. 4: COMMONLY USED DISINTEGRANTS

DISINTEGRANTS	CONCENTRATION IN GRANULES (%W/W)	SPECIAL COMMENTS
Starch USP	5-20	Higher amount is required, poorly compressible
Starch 1500	5-15	-
Avicel®(PH 101, PH 102)	10-20	Lubricant properties and directly compressible
Solka floc®	5-15	Purified wood cellulose
Alginic acid	1-5	Acts by swelling
Na alginate	2.5-10	Acts by swelling
Explotab®	2-8	Sodium starch glycolate, superdisintegrant.
Polyplasdone®(XL)	0.5-5	Crosslinked PVP
Amberlite® (IPR 88)	0.5-5	Ion exchange resin
Methyl cellulose, Na CMC, HPMC	5-10	-
AC-Di-Sol®	1-3	Direct compression
2-4	Wet granulation	
Carbon dioxide	-	Created *insitu* in effervescent tablet

SUPERDISINTEGRANTS

As days passes, demand for faster disintegrating formulation is increased. So, pharmacist needs to formulate disintegrants i.e. Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. But have one drawback that it is hygroscopic therefore not used with moisture sensitive drugs.

Superdisintegrants break a tablet into smaller fragments increasing the surface area of the dosage form and the rate of drug absorption. Ac-Di-Sol® Croscarmelose sodium was developed to:

- Enhance drug dissolution by speeding tablet disintegration
- Provide the highest level of disintegration force at low use levels

Utilize dual disintegration mechanisms of wicking and swelling for more rapid disintegration.

And this superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

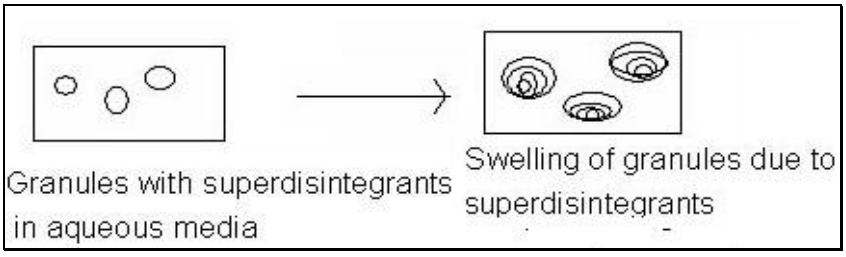


FIGURE NO. 4: MECHANISM OF SUPERDISINTEGRANTS BY SWELLING

TABLE NO. 5: COMMONLY USED SUPERDISINTEGRANTS

SUPERDISINTEGRANTS	MECHANISM OF ACTION	SPECIAL COMMENT
Croscarmelose Ac-Di-Sol Primellose Solutab Vivasol	Swells 4-8 folds in < 10 seconds. Swelling and wicking both	Swells in two dimensions. Direct compression or granulation Starch free
Crospovidone Crospovidon M Kollidon Polyplasdone	Swells very little and returns to original size after compression but act by capillary action	Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab Primogel	Swells 7-12 folds in <30 seconds	Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine	Rapid swelling in aqueous medium or wicking action	Promote disintegration in both dry or wet granulation
Soy polysaccharides Emcosoy		Does not contain any starch or sugar. Used in nutritional products.
Calcium silicate	Wicking action	Highly porous, light weight optimum concentration is between 20-40%

FACTORS AFFECTING DISINTEGRATION

EFFECT OF FILLERS

The solubility and compression characteristics of fillers affect both rate and mechanism of disintegration of tablet. If soluble fillers are used then it may cause increase in viscosity of the penetrating fluid which tends to reduce effectiveness of strongly swelling disintegrating agents and as they are water soluble, they are likely to dissolve rather than disintegrate. Insoluble diluents produce rapid disintegration with adequate amount of disintegrants. Chebli and Cartilier proved that tablets made with spray dried lactose (water soluble filler) disintegrate more slowly due to its amorphous character and has no solid planes on which the disintegrating forces can be exerted than the tablet made with crystalline lactose monohydrate.

EFFECT OF BINDER

As binding capacity of the binder increases, disintegrating time of tablet increases and this counteract the rapid disintegration. Even the concentration of the binder can also affect the disintegration time of tablet.

EFFECT OF LUBRICANTS

Mostly lubricants are hydrophobic and they are usually used in smaller size than any other ingredient in the tablet formulation. When the mixture is mixed, lubricant particles may adhere to the surface of the other particles. This hydrophobic coating inhibits the wetting and consequently tablet disintegration. Lubricant has a strong negative effect on the water uptake if tablet contains no disintegrants or even high concentration of slightly swelling disintegrants. On the contrary, the disintegration time is hardly affected if there is some strongly swelling disintegrants are present in the tablet. But there is one exception like sodium starch glycolate whose

effect remains unaffected in the presence of hydrophobic lubricant unlike other disintegrants.

EFFECT OF SURFACTANTS

Sodium lauryl sulphate increased absorption of water by starch or had a variable effect on water penetration in tablets. Surfactants are only effective within certain concentration ranges. Surfactants are recommended to decrease the hydrophobicity of the drugs because the more hydrophobic the tablet the greater the disintegration time.[7,8]

PREFORMULATION STUDIES

It is an investigation of physical and chemical properties of the new compound (drug) that could affect drug performance and development of an efficacious dosage form. Thus preference is the basis for effective formulation and drug stability.

Major areas of Preformulation Research

I. Bulk Characterization

a. Crystallinity and Polymorphism
b. Hygroscopy
c. Fine particle characterization
d. Bulk density
e. Powder flow properties

II. Solubility analysis

a. Ionization constant pKa
b. pH solubility profile
c. Common ion effect
d. Thermal effects
e. Solubilization
f. Partition coefficient
g. Dissolution

III. Stability analysis

a. Stability in toxicology formulations
b. Solution stability
c. pH rate profile
d. Solid state stability
e. Bulk stability
f. Compatibility

DERIVED PROPERTIES OF POWDERS

POROSITY: Influences the dissolution of the drug

BULK DENSITY: Helps in selecting containers for packing a dosage form

FLOW PROPERTIES: Helps in maintaining a uniform weight of tablets or capsules during production.[6]

ANGLE OF REPOSE: Angle of repose was determined by using funnel method. The accurately weighted blend was taken in a funnel. The height of the funnel was adjusted in such was that the tip of the funnel just touches the apex of the heap of blend. The drug excipient blend/granules were allowed to follow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$tan\,\theta = \frac{h}{r}$$

Where h and r are the height and radius of the powder cone.

TABLE NO. 6: ANGLE OF REPOSE

Angle of repose (θ)	Type of flow
25 - 30	Excellent
31 – 35	Good
36 – 40	Fair- aid not needed
41 – 45	Passable – may hang up
46 – 55	Poor – must agitate, vibrate
56 – 65	Very poor
>66	Very, very poor

BULK DENSITY AND TAPPED DENSITY

The bulk density of a solid is often very difficult to measure since the slightest disturbance of the bed may result in a new bulk density. Moreover, it is clear that the bulking properties of a powder are dependent on the "history" of the powder (E.g. How it was handled), and that it can be packed to have a range of bulk densities. Thus, it is essential in reporting bulk density to specify how the determination was made.

Because the interparticulate interactions that influence the bulking properties of a powder are also the interactions that interfere with powder flow, a comparison of the bulk and tapped densities can give a measure of the relative importance of these interactions in a given powder to flow. The bulk density often is the bulk density of the powder as poured" or as passively filled into a measuring vessel. The tapped density is a limiting density attained after "tapping down" usually in a device that lifts and drops a volumetric measuring cylinder containing the powder a fixed distance.

BULK DENSITY

Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a

graduated cylinder (method I) or through a volume measuring apparatus into a cup (method II)

$$\frac{M}{V_0}$$

Where, M = weight of API/granules

V_0 = unsettled apparent volume

TAPPED DENSITY

Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped and volume readings are taken until little further volume change is observed. The mechanical tapping is achieved by raising the cylinder and allowing it to drop under its own weight a specified distance by either of two methods as described below. Devices that rotate the cylinder during tapping may be preferred to minimize any possible separation of the mass during tapping down.

$$\frac{M}{V_f}$$

Where, M = Weight of API/ granules,

V_f = tapped volume

COMPRESSIBILITY INDEX AND HAUSNER RATIO

The compressibility index and Hausner ratio are measures of the property of a powder to be compressed. As such, they are measures of the relative importance of interparticulate interaction. In a free flowing powder, such interactions are generally less significant and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently grater interparticle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility and Hausner ratio.

The compressibility index and the closely related Hausner ratio become the simple, fast, and popular method of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials because all of these can influence the observed compressibility index. The compressibility index and Hausner's ratio are determined by measuring both the bulk volume and tapped volume of the powder.

BASIC METHODS FOR COMPRESSIBILITY INDEX AND HAUSNER'S RATIO

The basic procedure is to measure (1) the unsettled apparent volume, V_0, and (2) the final tapped volume, V_f, of the powder after tapping the material until no further volume change occur. The compressibility index and Hausner's ratio are calculated as follows.

$$\text{Compressibility Index} = 100 \times \left(\frac{V_o - V_f}{V_0} \right)$$

$$\text{Hausner ratio} = \frac{V_o}{V_f}$$

Alternatively the compressibility index and Hausner ratio may be calculated using measured value for bulk density (ρ_{tapped}) as follow

$$\text{Compressibility Index} = 100 \times \left(\frac{\rho_{tapped} - \rho_{Bulk}}{\rho_{tapped}} \right)$$

$$\text{Hausner ratio} = \left(\frac{\rho_{tapped}}{\rho_{Bulk}} \right)$$

TABLE NO. 7: SCALE OF FLOW ABILITY[9,10]

Compressibility index (%)	Flow character	Hausner Ratio
<10	Excellent	1.00 – 1.11
11 – 15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25
21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	1.34 – 1.45
32 – 37	Very poor	1.46 – 1.59
>38	Very, Very poor	>1.60

STABILITY STUDIES

The purpose of stability testing is to investigate how the quality of a drug product changes with time under the influence of environmental factors such as temperature, humidity and light and to establish a shelf life for the drug product and to recommend storage conditions.

Pharmaceutical regulatory agencies world-wide demand that the product retains its identity, quality, purity and potency for the time the product is commercially available. Consequently, the agencies expected to see the stability data supporting the proposed expiration date of the product in the marketing submission.

Various stability guidelines have been published over the last 5 years describing the type of studies and type of data needed to satisfy regulatory agencies world wide. Currently the guidelines promulgated by the International Conference on Harmonization (ICH) are the most commonly accepted. In the broadest sense, the stability studies that are conducted should provide evidence of how the quality of the drug

substance and drug product changes over time when subjected to various environmental conditions, such as temperature, humidity and light.

Some of the important definitions as per ICH guidelines used to facilitate interpretation of the guidelines as follows:

FORMAL STABILITY STUDIES

Long term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of a drug substance or the shelf life of a drug product.

LONG TERM TESTING / REAL TIME TESTING

Stability studies under the recommended storage condition for the re-test period or shelf life proposed or approved for labeling.

INTERMEDIATE TESTING

Studies conducted at 30°C / 65% RH and designed to moderately increase the rate of chemical degradation or physical changes for a drug substance or drug product intended to be stored long term at 25°C.

ACCELERATED TESTING

Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

CLIMATIC ZONES

The four zones in the world that are distinguished by their characteristic prevalent annual climatic conditions. This is based on the concept described by W. Grimm.

DOSAGE FORM

A pharmaceutical product type (E.g.: tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

DRUG PRODUCT

The dosage from in the final immediate packaging intended for marketing.

DRUG SUBSTANCE

The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.

EXPIRATION DATE

The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification if stored under defined conditions, and after which is must not be used.

NEW DRUG SUBSTANCE

The designed therapeutic moiety, which has no previously been registered in a region or member state (also referred to as a new molecular entity or new chemical entity). It may be a complex, simple ester, or salt of a previously approved drug substance.

NEW DRUG PRODUCT

A pharmaceutical product type, for example, tablet, capsule, solution, cream etc., which has not previously been registered in a region or member state, and which contains a drug ingredient generally, but not necessarily in association with excipients.

DEGRADATION PRODUCT

A molecule resulting from a chemical change in the drug molecule brought about over time and/or by the action of e.g. light, temperature, pH, water, or by reaction with a excipient and/or the immediate container/closure system. Also called decomposition product.

IMPURITY

1) Any component of the new drug substance which is not the chemical entity defined as the new drug substance.
2) Any components of the drug product which is not the chemical entity defined as the drug substance or an excipient in the drug product.

IMMEDIATE RELEASE

Allows the drug to dissolve in the gastrointestinal contents, with the intention of delaying or prolonging the dissolution or absorption of the drug.

In general stability studies are classified into

1. Real time or long time
2. Intermediate
3. Accelerated

Based on the place (zone) of study the stability studies are selected.

TABLE NO. 8: CLIMATIC ZONE AND STORAGE CONDITIONS

Climate zone	Conditions	Derived storage condition
I	Temperature	21°C / 45% RH
II	Mediterranean, subtropical	25°C / 45% RH
III	Hot, dry	30°C / 45% RH
IV	Hot, humid	30°C / 45% RH

TABLE NO. 9: TESTING FREQUENCY[11,12]

Study	Storage condition	Intervals (months)/minimum time period covered by data at submission
Long term	25°C ± 2°C / 60% ± 5% RH[a]	3, 6, 9, 12, 18, 24, 36 / minimum 12 months
Intermediate*	30°C ± 2°C / 65% ± 5% RH	6, 9[b], 12[b] minimum 6 months
Accelerated	40°C ± 2°C / 75%[c] ± 5% RH	1, 3, 6 / minimum 6 months

* If 30°C ± 2°C / 65% RH ± 5% RH is a long term condition, there is no intermediate condition.

[a] Zone II, 30°C / 35% RH for Zone III, and 30° C / 70% RH for Zone IV.

[b] Test 9 and 12 months only if failure to meet specification at 40°C /75% RH or assay is different from initial by greater than 5%.

[c] FDA's generic schedule requires testing at 1, 2 and 3 months.

NON STEROIDAL ANTI-INFLAMMATORY DRUGS
(NSAIDs) - A Brief Review

The anti-inflammatory, analgesic and anti pyretic drugs are a heterogeneous group of compounds often chemically unrelated (although most of them are organic acids), which nevertheless share certain therapeutic actions and side effects. These are called NSAIDs.

Algesia (pain)

Algesia is an ill- defined unpleasant sensation usually evoked by an external or internal noxious stimulus.

Analgesic

A drug that selectively relieves pain by acting in the CNS, or on peripheral pain mechanism with out altering the consciousness.[13]

DISCOVERY OF NSAIDs

The development of the first of the category of what are know as the non steroidal anti-inflammatory drugs (NSAIDs) of which Aspirin was recognized as progenitor, was Phenylbutazone in 1946 and Indomethacin in 1960's[14] and later Etodolac in 1970's[2]. Phenylbutazone was initially employed as a combination with antipyrine. However, it has greater analgesic and anti-inflammatory activity than antipyrine and was the best part of 30 years successfully used for arthritic and other painful inflammatory conditions.

INTRODUCTION OF INFLAMMATION

Prostaglandins belong to a group of compounds known as eicosanoids. Eicosanoids are breakdown products of the polyunsaturated fatty acids (e.g., arachidonic acid) of the plasmalemmal phospholipids. When cell membranes are damaged, arachidonic acid is liberated into the cytoplasm where it serves as a substrate for the lipoxygenases (e.g., 5-

lipoxygenase), cyclooxygenases (e.g., prostaglandin synthase, prostaglandin H (synthase), and other enzymes [Figure No. 5].

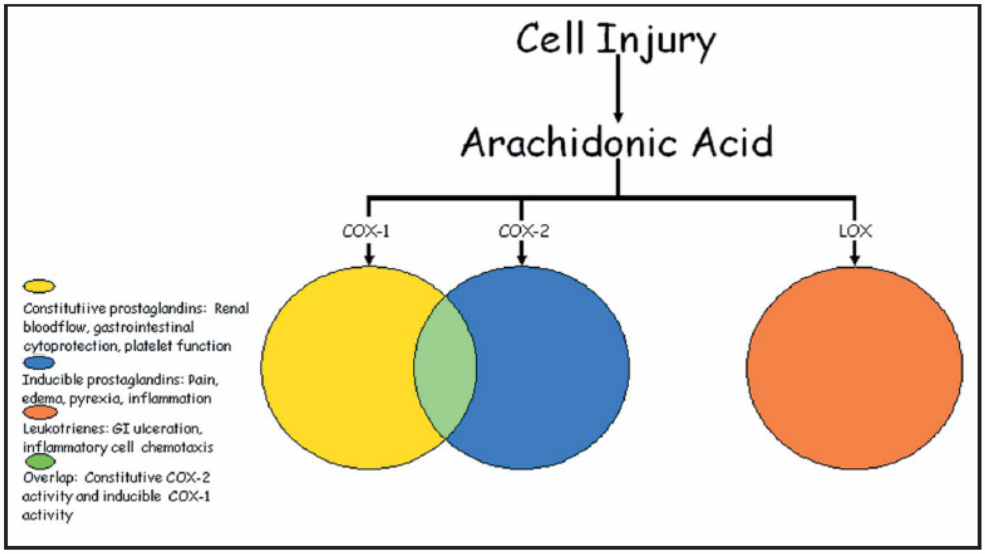


FIGURE NO. 5: SCHEMATIC DEPICTING THE ROLES OF CYCLOOXYGENASE (COX)-1, COX-2, AND LIPOXYGENASE (LOX) IN THE LIBERATION OF INFLAMMATORY MEDIATORS VIA THE ARACHIDONIC ACID CASCADE.

Although there are three mammalian lipoxygenases, the one with the most clinical significance is 5-lipoxygenase. It is 5-lipoxygenase that is responsible for the conversion of arachidonic acid to 5-hydroperoxyeicosatetraenoicacid, which is then enzymatically converted to leukotriene A4 (LTA4). Leukotriene A4 is the precursor molecule for the other leukotrienes and can be enzymatically converted to leukotriene B4 (LTB4), which attracts many cells of myeloid origin. Cyclooxygenase 1-related prostaglandins (i.e., constitutive prostaglandins) are produced by many tissues and participate in the maintenance of a variety of physiological effects (e.g., protection of gastrointestinal [GI] mucosa, maintenance of renal blood flow, hemostasis). Cyclooxygenase 2, on the other hand, is the isoform primarily responsible for the production of inducible prostaglandins [Figure No. 5].

As such, COX-2-related prostaglandins are considered to be "nonphysiologic" and represent a clinically and therapeutically relevant group of compounds primarily involved in inflammation. Vasodilatation, changes in capillary permeability, potentiation of other chemical mediators of inflammation (e.g., histamine), chemotaxis, and hyperalgesia are all aspects of inflammation that are initiated and perpetuated by the presence of COX-2-related prostaglandins. It is important to note that COX-1 and COX-2 are also structurally distinct. They have different numbers of amino acids and sequences, as well as different morphologies. A smaller valine at the 523 position of COX-2 gives access to a "side pocket" unique to COX-2. This side pocket is exploited as the binding site for NSAIDs that preferentially bind with COX-2.

MECHANISMS OF ACTION OF NSAIDs

Nonsteroidal anti-inflammatory drugs block the production of prostaglandin by binding to and obstructing the action of cyclooxygenase, an interaction that is contingent upon both the drug and dose chosen. The therapeutic, toxic, and anti-inflammatory properties of different NSAIDs are directly related to the amount and type of prostaglandin production that is impeded. Based on the nature and physiological actions of COX-1 and COX-2, the NSAIDs that preferentially block the production of COX-2-related prostaglandins may be clinically superior to those with less COX-2 selectivity. Nonsteroidal anti-inflammatory drugs that inhibit COX-2 may be more desirable, because they inhibit the formation of COX-2 prostaglandins that are responsible for the clinical signs associated with inflammation, and because they do not have as much effect on the COX-1 prostaglandins, which have many heomostatic properties. The specificity of a drug for a given isoform of COX is typically reported as a ratio. A COX-2:COX-1 ratio <1.0 has traditionally been sought, as this ratio

indicates that a given NSAID preferentially inhibits COX-2 (i.e., less drug is required to inhibit COX-2 than is needed to inhibit COX-1 activity).[15]

CLASSIFICATION OF NSAIDs[13]

The various analgesic-antipyretic anti-inflammatory agents are classified as

1. **Acidic Drugs**
   - Salicylates: E.g. Salicylic acid, Aspirin.
   - Para-amino phenols: E.g.: Paracetamol.
   - Pyrazolones: E.g.: Phenylbutazone, Suxibuzone.
   - Indole acetic acids: E.g.: Indomethacin, Clamidoxic acid.
   - Propionic acids: E.g.: Ibuprofen, Diclofenac.
   - Aryl anthranilic acids: E.g.: Meclofenamic acid, Tolfenamic acid.
   - Miscellaneous agents: E.g.: Piroxicam, Fenoxicam.
2. **Basic Drugs** E.g.: Timegadine inhibits neutrophil degranulation and superoxide production.
3. **Non-Acidic Drugs** E.g.: Indoxole Nictimodole.

CLASSIFICATION OF NSAIDs BY CHEMICAL STRUCTURE

1. **Carboxylic Acid Groups**
   - Salicylates (Acetylsalicylate, Choline Salicylate, Diflunisal, Magnesium choline Salicylate, Magnesium Salicylate, Salsalate).
   - Acetic Acids (Diclofenac Sodium, Diclofenac Potassium, Etodolac, Indomethacin, Ketorolac, Nabumetone, Sulindac, Tolmetin).
   - Propionic acids (Carprofen, Fenoprofen, Flurbiprofen, Ibuprofen, Ketoprofen, Loxoprofen, Naproxen, Naproxen sodium, Oxaprozin, Vedaprofen).

- Anthranilic acids (Meclofenamic acid, Meclofenamate sodium, Tolfenamic acid).
- Phenlylacetic acids (Acetaminophen).
- Amino nicotinic acids (Flunixin).
- Indole Analogs (Indomethacin, Nabumetone, Ketorolac, Etodolac).

2. **Enolic Acid Groups** (which doesn't have carboxylic group but acid due to the enolic Hydroxyl substituent):
   - Pyrazolones (Phenylbutazone, Oxyphenbutazone, Dipyrone, Ramifenazone).
   - Oxicams (Aceclofenac, Piroxicam, Tenoxicam).
3. **Coxibs** Celecoxib, Rofecoxib, Valdecoxib, Parecoxib, Etoricoxib.
4. **Gold Salts** Auranofin, Gold sodium thiomalate, Aurothioglucose.

TABLE NO. 10: SIDE EFFECTS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)[16]

Serious side effects include	Other side effects include
• heart attack • stroke • high blood pressure • heart failure from body swelling (fluid retention) • kidney problems including kidney failure • bleeding and ulcers in the stomach and intestine • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • liver problems including liver failure • asthma attacks in people who have asthma	• constipation • stomach pain • diarrhea • gas • heartburn • nausea • vomiting • dizziness

Get emergency help right away if you have any of the following symptoms:

• shortness of breath or trouble breathing • chest pain	• slurred speech • swelling of the face or throat

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:

• nausea • more tired or weaker than usual • itching • your skin or eyes look yellow • stomach pain • flu-like symptoms • vomit blood	• there is blood in your bowel movement or it is black and sticky like tar • unusual weight gain • skin rash or blisters with fever • swelling of the arms and legs, hands and feet

TABLE NO. 11: NSAID MEDICINES THAT NEED A PRESCRIPTION[16]

Generic Name	Trade name
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol)
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbiprofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen (combined with hydrocodone), Combunox
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naproxyn, Naprelan, Naprapac
Oxaprozin	Daypro

DRUG PROFILE

ETODOLAC[2,17]

Etodolac is a member of the pyranocarboxylic acid group of Non Steroidal Anti-Inflammatory Drug (NSAID). Etodolac is a racemic mixture of [+] S and [-] R-enantiomers.

CHEMICAL NAME: (±) 1, 8-diethyl-1, 3, 4, 9,-tetrahydropyrano-[3,4-b]indole-1-acetic acid.

NONPROPRIETARY NAMES / SYNONYMS: Etodolac, Etodolic acid, Etodolaco; Etodolacum; Etodolák; Etodolak; Etodolaakki; Etodolakas.

PROPRIETARY NAMES: Lodine, Ramodar, Ultradol, Zedolac, Edolan.

EMPIRICAL FORMULA: $C_{17}H_{21}NO_3$.

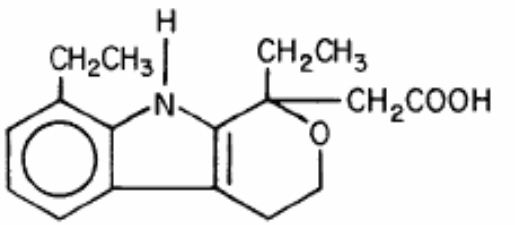
MOLECULAR WEIGHT: 287.37.

CAS NUMBER: 41340-25-4.

MELTING POINT: 144°C to 150°C.

pKa AND n-OCTANOL:WATER PARTITION COEFFICIENT: 4.65 and 11.4 at pH 7.4.

CHEMICAL STRUCTURE:



ELEMENTAL ANALYSIS: The calculated elemental composition is as follows

Carbon: 71.06%, Oxygen: 16.70%, Hydrogen: 7.37%, Nitrogen: 4.87%

DESCRIPTION: Etodolac is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol.

INDICATIONS: Analgesic; anti-inflammatory; antipyretic.

PREPARATIONS AVAILABLE WORLDWIDE FOR ETODOLAC[16]

TABLE NO. 12: PREPARATIONS AVAILABLE WORLDWIDE FOR ETODOLAC

Brand Name	Company Name	Country Name
Eccoxolac	Viatris	United Kingdom
Etonox	Charoen	Thailand
Flancox	Apsen	Brazil
Lodine	Sankyo	France
Lodine	Wyeth	Hong Kong
Lodine	Wyeth	Venezuela
Lodine	Wyeth Lederle	Italy
Lonene	Sunthi Sepuri	Indonesia
Sodolac	Sofex	Portugal
Ultradol	Procter and Gamble	Canada
Ecridoxan	Help	Germany
Etopan	Taro	Israel
Hypen	Shinyaku	Japan
Lodine	Shire	United Kingdom
Lodine	Wyeth	Mexico
Lodine	Wyeth-Ayerst	USA
Lodine	Wyeth LederlePort.	USA
Lonine	Wyeth	Germany
Tadolak	Saba	Turkey
Zedolac	Maggioni	Italy

Brand Name	Company Name	Country Name
Edolan	Lepetit	Italy
Etol	Nobel	Turkey
Etopan	Winthrop	United Kingdom
Lodine	Algol	Finland
Lodine	Sigma-Tau	Switzerland
Lodine	Wyeth	Turkey
Lodine	Wyeth Lederle	Austria
Lodot	BA Farma	Portugal
Metazin	Clintex	Portugal
Todolac	Norpharma	Denmark
Dualgan	ITF	Portugal

PHARMACOKINETICS

ABSORPTION

- Onset and Duration of action

Onset of action:

- Initial response – Analgesia, Regular release is 30 minutes.
- Peak response – Analgesia, Regular release is 1 to 2 hours.

Duration of action:

- Single dose – Analgesia, Regular release is 4 to 5 hours.

- Drug Concentration levels

Time to Peak Concentration:

- Oral, Regular release is 1 to 2 hours.
- Oral, Extended release is 3 to 12 hours.

Peak Concentration are dose-proportional for both free and total Etodolac following 400 mg every 12 hours, following 600 mg, the peak

is approximately 20% higher than expected on the basis of the lower doses.

- Bioavailability
    - Oral, Regular release is 80% to 100%.
    - Oral, Extended release is 78% to 84%.
- Effects of Food

Clinically significant:

- The peak concentration is 50% and the time to reach peak concentration is increased by about 1.4 to 3.8 hours.
- When Etodolac extended-release is administered with food, peak serum concentrations occurs earlier at 1.5 to 6 hours.
- High-fat meals do not affect the absorption of Etodolac extended-release.

DISTRIBUTION

- Distribution sites: Protein Binding - 99%
- Distribution Kinetics
    - Distribution Half-Life – 0.71 hours.
    - Volume of distribution – 362 ml/kg, Etodolac exhibit two compartment pharmacokinetics, the Vd of the central compartment is 132 ml/kg.

METABOLISM

- Metabolism Sites and Kinetics: Liver, extensive.
- Metabolism:
    - Glucuronide metabolite, inactive.
    - Hydroxylated metabolite, inactive.
    - Glucuronidated hydroxylated metabolite, inactive.

EXCRETION

- Kidney
  - Renal Excretion (%) – 72 %.
  - About 1% of a dose is excreted as unchanged drug, the remainder is excreted as metabolites.
- Others: Feces, 16%
- Elimination Half-life: 6 to 7 hours.

DOSING INFORMATION

- **Osteoarthritis**
  - Initial: Immediate release, 300 mg orally two or three times day or 400 to 500 mg orally two times a day.
  - Maintenance: Extended release, 400 to 1000 mg orally once a day, immediate release, 600 to 1000 mg/day orally divided 2 to 4 times maximum dose 1200 mg/day.
- **Pain**
  - Immediate release, 200 to 400 mg orally every 6 to 8 hours as needed, maximum dose 1200 mg/day.
- **Rheumatoid Arthritis**
  - Initial: Immediate Release, 300 mg orally two or three times a day or 400 to 500 mg orally two times a day.
  - Maintenance: Extended Release, 400-1000 mg orally once a day. Immediate Release, 600-1000 mg/day orally divided 2-4 times. Maximum dose 1200 mg/day.
- **Adults**
  - Use lowest effective dose for shortest possible duration.
  - After observing initial response, adjust dose and frequency to meet individual patient's needs.
- **Pediatrics**
  - Not FDA approved for children less than 6 years old.

- Use lowest effective dose for shortest possible duration.
- After observing initial response, adjust dose and frequency to meet individual patient's needs.

DOSAGE IN RENAL FAILURE: No dosage adjustment of Etodolac is necessary in patients with mild-to-moderate renal failure. However, Etodolac should be used with caution because it may cause cumulative effects on renal function especially in patients with pre-existing mild-to-moderate renal dysfunction.

DOSAGE IN HEPATIC INSUFFICIENCY: In patients with compensated hepatic cirrhosis, the dose of Etodolac does not need to be adjusted. However, the dose may need to be decreased in patients with severe hepatic failure.

DOSAGE IN GERIATRIC PATIENTS: The dose of Etodolac does not need to be adjusted in elderly patients; however, it should be used cautiously since the elderly are more sensitive to the side effects.

CONTRAINDICATIONS

- Treatment of pre-operative pain in setting of coronary artery bypass graft (CABG) surgery.
- Hypersensitivity to Etodolac.
- Patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other nonsteroidal anti-inflammatory agents; severe, even fatal, anaphylactic-like reactions have been reported.

TABLE NO. 13: ADVERSE EFFECTS OF ETODOLAC

Serious side effects include	Other side effects include
Heart attack, Stroke, High blood pressure, Heart failure from body swelling(fluid retention), kidney problems, Bleeding and Ulcer in the stomach and intestine, Low red blood cells(anemia), Shortness of breath or trouble breathing, Chest pain, Weakness in one part or side of your body, flu- like symptoms.	Stomach pain, Constipation, Diarrhea, Slurred speech, Swelling of the face or throat, unusual weight gain, skin rash or blisters with fever, Skin rash or blisters with fever, swelling of the arms and legs, hands and feet

DRUG INTERACTIONS

ACE-INHIBITORS

- **Alacepril** - Interaction Effect is decreased Antihypertensive and natriuretic effects and probable mechanism is interference with production of vasodilator and natriuretic prostaglandins.

ASPIRIN

When Etodolac is administered with aspirin, its protein binding is reduced, although the clearance of free Etodolac is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of Etodolac and aspirin is not generally recommended because of the potential of increased adverse effects.

ANTACIDS

The concomitant administration of antacids has no apparent effect on the extent of absorption of Etodolac. However, antacids can decrease the peak concentration reached by 15% to 20% but have no detectable effect on the time-to-peak.

DIURETICS

Etodolac has no apparent pharmacokinetic interaction when administered with furosemide or hydrochlorothiazide. Nevertheless, clinical

studies, as well as post marketing observations have shown that Etodolac can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure.

GLYBURIDE

Etodolac has no apparent pharmacokinetic interaction when administered with glyburide.

LITHIUM

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

PHENYLBUTAZONE

Phenylbutazone causes increase (by about 80%) in the free fraction of Etodolac. Although in vivo studies have not been done to see if Etodolac clearance is changed by co-administration of phenylbutazone, it is not recommended that they be co administered.

PHENYTOIN

Etodolac has no apparent pharmacokinetic interaction when administered with phenytoin.

WARFARIN

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than that of users of either drug alone. Short-term pharmacokinetic studies have demonstrated that concomitant administration of warfarin and Lodine® (Etodolac capsules and tablets) results in reduced protein binding

of warfarin, but there was no change in the clearance of free warfarin. There was no significant difference in the pharmacodynamic effect of warfarin administered alone and warfarin administered with Etodolac as measured by prothrombin time. Thus, concomitant therapy with warfarin and Etodolac should not require dosage adjustment of either drug. However, caution should be exercised because there have been a few spontaneous reports of prolonged prothrombin times, with or without bleeding, in Etodolac-treated patients receiving concomitant warfarin therapy.

CYCLOSPORINE, DIGOXIN, METHOTREXATE

Etodolac, like other NSAIDs, through effects on renal prostaglandins, may cause changes in the elimination of these drugs leading to elevated serum levels of cyclosporine, digoxin, methotrexate, and increased toxicity. Nephrotoxicity associated with cyclosporine may also be enhanced. Patients receiving these drugs who are given Etodolac, or any other NSAID, and particularly those patients with altered renal function, should be observed for the development of the specific toxicities of these drugs. NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

SAFETY PROFILE OF ETODOLAC

- Etodolac is a nonsteroidal anti-inflammatory drug (NSAIDs) of the pyranocarboxylic acid class developed in the 1970s.[2]
- Etodolac is a synthesized anti-inflammatory drug with potent inhibitory activity against interleukin-1 beta (IL-1beta)-induced prostaglandin E2 biosynthesis in chondrocytes.

- Since gastrointestinal (GI) complaints and blood loss are frequently associated with the use of anti-inflammatory agents, several studies have been conducted to assess the effect of Etodolac on the GIT.
- The pharmacological activities and ulcerogenicity of Etodolac compare with six other nonsteroidal anti-inflammatory drugs: Indomethacin, Diclofenac Sodium, Piroxicam, Naproxen, Ketoprofen and Aspirin.
- The safety margin of Etodolac was calculated from ED_{50} value for the primary inflammation of adjuvant arthritis, the ED_{50} value for the secondary inflammation of adjuvant arthritis and the acetic acid induced writhing were highest among the 7 drugs. These results indicate that safety margins for Etodolac are high.
- The ulcerogenic action of the anti-inflammatory drugs is due to the inhibition of prostaglandin biosynthesis in the stomach. Etodolac showed the lowest ulcerogenicity among the 7 drugs tested.
- This weak ulcerogenic activity may be derived from the weak inhibitory activity of Etodolac on prostaglandin biosynthesis in the gastric mucosa.
- These results suggest that Etodolac is useful in the clinical treatment of rheumatoid arthritis. Etodolac did not show an analgesic effect on non-inflammatory pain in the normal paws of rats and an antipyretic effect on the rectal temperature of normal rats.
- Etodolac is considered, overall, to be an anti-inflammatory drug with potent antiarthritic activity and weak ulcerogenic activity.[4]
- As a COX-2 selective inhibitor, Etodolac can not only enhance its anti-inflammatory and analgesic activity but also improve patient compliance.[18]

- Etodolac, with an effective anti-inflammatory dose, no sustained effects on renal function were found in either normal or renal-impaired patients.[19]
- The most frequently used NSAIDs are shown in descending order in Figure No. 6.[20]

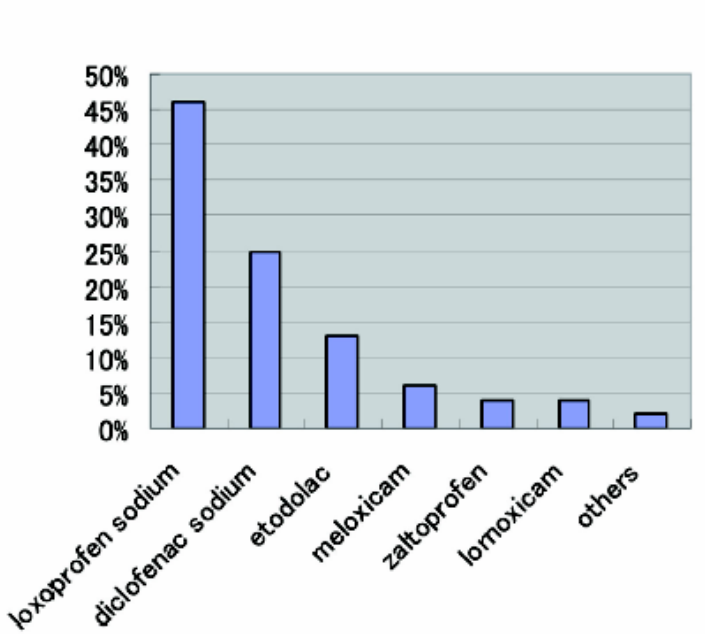


FIGURE NO. 6: RATIO OF PRESCRIPTION OF COMMON NSAIDS

EXCIPIENT PROFILE[21]

CROSPOVIDONE

NONPROPRIETARY NAMES

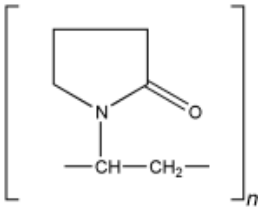
- BP : Crospovidone
- PhEur : Crospovidonum
- USPNF : Crospovidone

SYNONYMS: Crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10; Polyvinylpolypyrrolidone; PVPP;

CHEMICAL NAME AND CAS REGISTRY NUMBER: 1-ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

EMPIRICAL FORMULA AND MOLECULAR WEIGHT: $(C_6H_9NO)_n$ >1 000 000.

STRUCTURAL FORMULA



FUNCTIONAL CATEGORY: Tablet Disintegrant.

APPLICATIONS IN PHARMACEUTICAL FORMULATION: Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone

can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

DESCRIPTION: Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

TYPICAL PROPERTIES:

Solubility: Practically insoluble in water and most common organic solvents.

STABILITY AND STORAGE CONDITIONS: Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

INCOMPATIBILITIES: Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adduct with some materials.

SAFETY: Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. Short-term animal toxicity studies have shown no adverse effects associated with crospovidone. However, owing to the lack of available data, an acceptable daily intake in humans has not been specified by the WHO.

LD_{50} (mouse, IP): 12 g/kg

HANDLING PRECAUTIONS: Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

SODIUM STARCH GLYCOLATE

NONPROPRIETARY NAMES

- BP : Sodium starch glycollate
- PhEur : Carboxymethylamylum natricum
- USPNF : Sodium starch glycolate

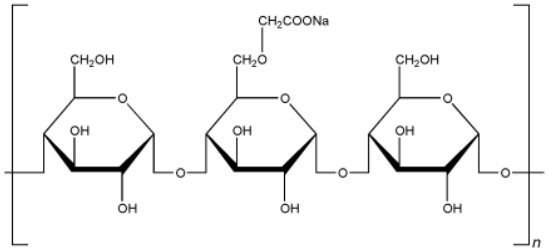
SYNONYMS: Carboxymethyl starch, Sodium salt; Explosol*;* Explotab*;* Glycolys*;* Primojel; starch carboxymethyl ether, sodium salt.

CHEMICAL NAME AND CAS REGISTRY NUMBER: Sodium carboxymethyl starch [9063-38-1]

EMPIRICAL FORMULA AND MOLECULAR WEIGHT

The molecular weight is typically 5×10^5–1×10^6.

STRUCTURAL FORMULA



FUNCTIONAL CATEGORY: Tablet and Capsule Disintegrant.

APPLICATIONS IN PHARMACEUTICAL FORMULATION: Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Sodium starch glycolate has also been investigated for use as a suspending vehicle.

DESCRIPTION: Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. The PhEur 2005 states that it consists of oval or spherical granules, 30–100 µm in diameter, with some less-spherical granules ranging from 10–35 µm in diameter.

TYPICAL PROPERTIES: Solubility: Sparingly soluble in ethanol (95%); practically insoluble in water. At a concentration of 2% w/v sodium starch glycolate disperses in cold water and settles in the form of a highly hydrated layer.

STABILITY AND STORAGE CONDITIONS: Sodium starch glycolate is stable and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking. The physical properties of sodium starch glycolate remain unchanged for up to 3–5 years if it is stored at moderate temperatures and humidity.

INCOMPATIBILITIES: Sodium starch glycolate is incompatible with ascorbic acid.

SAFETY: Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

HANDLING PRECAUTIONS: Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium starch glycolate may be irritant to the eyes; eye protection and gloves are recommended. A dust mask or respirator is recommended for processes that generate a large quantity of dust.

MICROCRYSTALLINE CELLULOSE

NONPROPRIETARY NAMES

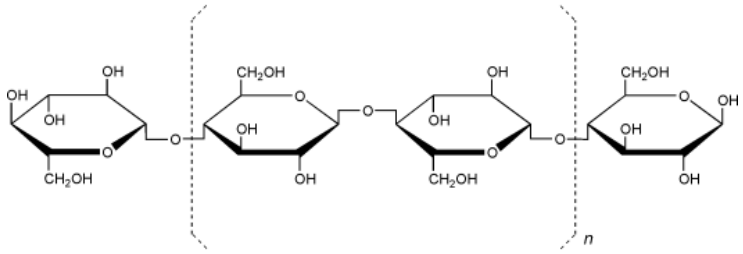
- BP : Microcrystalline cellulose
- JP : Microcrystalline cellulose
- PhEur : Cellulosum microcristallinum
- USPNF : Microcrystalline cellulose

SYNONYMS: Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel*;* Pharmacel; Tabulose; Vivapur*.*

CHEMICAL NAME AND CAS REGISTRY NUMBER: Cellulose [9004-34-6]

EMPIRICAL FORMULA AND MOLECULAR WEIGHT: $(C_6H_{10}O_5)_n$ ≈36 000. where $n \approx 220$.

STRUCTURAL FORMULA



FUNCTIONAL CATEGORY: Adsorbent; Suspending agent; Tablet and Capsule Diluent; Tablet Disintegrant.

APPLICATIONS IN PHARMACEUTICAL FORMULATION: Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products

Table No. 14: Uses of microcrystalline cellulose.

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluent	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

DESCRIPTION: Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially

available in different particle sizes and moisture grades that have different properties and applications.

TYPICAL PROPERTIES:

Solubility: Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

STABILITY AND STORAGE CONDITIONS: Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

INCOMPATIBILITIES: Microcrystalline cellulose is incompatible with strong oxidizing agents.

SAFETY: Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations. Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.

POVIDONE

NONPROPRIETARY NAMES

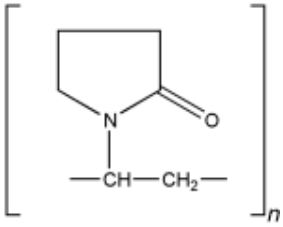
- BP : Povidone
- JP : Povidone
- PhEur : Povidonum
- USP : Povidone

SYNONYMS: E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; Polyvidone; Polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer**.**

CHEMICAL NAME AND CAS REGISTRY NUMBER: 1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

EMPIRICAL FORMULA AND MOLECULAR WEIGHT: $(C_6H_9NO)_n$ 2500–3 000 000

STRUCTURAL FORMULA



FUNCTIONAL CATEGORY: Disintegrant; Dissolution Aid; Suspending Agent; Tablet Binder.

APPLICATIONS IN PHARMACEUTICAL FORMULATION: In tableting, povidone solutions are used as binders in wet-granulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. Povidone solutions may also be used as coating agents. Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

TABLE NO. 15: USES OF POVIDONE

Use	Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5–5

DESCRIPTION: Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

TYPICAL PROPERTIES: Solubility: Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the *K*-value.

STABILITY AND STORAGE CONDITIONS: Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

INCOMPATIBILITIES: Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds. The efficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with povidone.

SAFETY: Povidone has been used in pharmaceutical formulations for many years, being first used in the 1940s as a plasma expander, although it has now been superseded for this purpose by dextran.Povidone is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes. Povidone additionally has no irritant effect on the skin and causes no sensitization.

A temporary acceptable daily intake for povidone has been set by the WHO at up to 25 mg/kg body-weight.

LD_{50} (mouse, IP): 12 g/kg

HANDLING PRECAUTIONS: Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

POLYOXYETHYLENE SORBITAN FATTY ACID ESTERS

NONPROPRIETARY NAMES

- BP : Polysorbate 20, Polysorbate 40, Polysorbate 60, and Polysorbate 80
- JP : Polysorbate 80
- PhEur : Polysorbatum 20, Polysorbatum 40, Polysorbatum 60, Polysorbatum 80
- USPNF : Polysorbate 20, Polysorbate 40, Polysorbate 60, and Polysorbate 80

SYNONYMS:

TABLE NO. 16: SYNONYMS OF SELECTED POLYSORBATES

POLYSORBATE	SYNONYMS
Polysorbate 20	Armotan PML 20; Capmul POE-L; Crillet 1; Drewmulse; E432; Durfax 20; Lamesorb SML-20; Liposorb L-20; Montanox 20; Norfox Sorbo T-20; sorbitan monododecanoate; Sorgen TW-20; T-Maz 20; polyoxyethylene 20 laurate; Protasorb L-20; Tween 20.
Polysorbate 40	Crillet 2; E434; Eumulgin SMP; Glycosperse S-20;; Lamesorb SMP-20; Liposorb P-20; Lonzest SMP-20; Montanox 40; Protasorb P-20; Ritabate 40; sorbitan monohexadecanoate; Sorbax PMP-20; Tween 40.
Polysorbate 60	Atlas 70K; Atlas Armotan PMS 20; Capmul POE-S; Crillet 3; Drewpone 60K; Durfax 60; Montanox 60; Polycon T 60 K; polyoxyethylene 20 stearate; Ritabate 60; Protasorb S-20; Sorbax PMS-20; T-Max 60KHS; Tween 60; Tween 60K; Tween 60.
Polysorbate 80	Atlas E; Armotan PMO 20; Capmul POE-O; Cremophor PS 80; Crillet 4; Crillet 50; Drewmulse POE-SMO; Drewpone 80K; Durfax 80; Durfax 80K; E433; Emrite 6120; Eumulgin SMO; Glycosperse O-20; Hodag PSMO-20; Liposorb O-20; Montanox 80; polyoxyethylene 20 oleate; -20; Tween 80.

CHEMICAL NAMES AND CAS REGISTRY NUMBERS

TABLE NO. 17: CHEMICAL NAMES AND CAS REGISTRY NUMBERS OF SELECTED POLYSORBATES

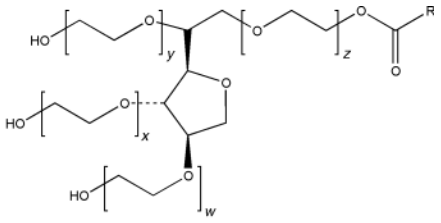
Polysorbate	Chemical name	CAS number
Polysorbate 20	Polyoxyethylene 20 sorbitan monolaurate	[9005-64-5]
Polysorbate 40	Polyoxyethylene 20 sorbitan monopalmitate	[9005-66-7]
Polysorbate 60	Polyoxyethylene 20 sorbitan monostearate	[9005-67-8]
Polysorbate 80	Polyoxyethylene 20 sorbitan monooleate	[9005-65-6]

EMPIRICAL FORMULA AND MOLECULAR WEIGHT

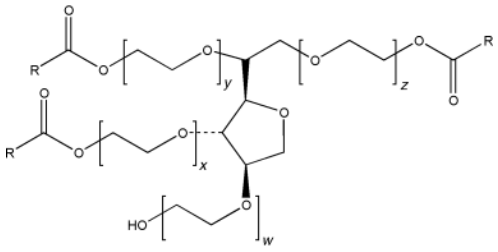
TABLE NO. 18: EMPIRICAL FORMULA AND MOLECULAR WEIGHT OF SELECTED POLYSORBATES

Polysorbate	Formula	Molecular weight
Polysorbate 20	$C_{58}H_{114}O_{26}$	1128
Polysorbate 40	$C_{62}H_{122}O_{26}$	1284
Polysorbate 60	$C_{64}H_{126}O_{26}$	1312
Polysorbate 80	$C_{64}H_{124}O_{26}$	1310

STRUCTURAL FORMULA



Polyoxyethylene sorbitan monoester



Polyoxyethylene sorbitan triester

FUNCTIONAL CATEGORY: Emulsifying agent; Nonionic Surfactant; Solubilizing Agent; Wetting and Suspending agent.

APPLICATIONS IN PHARMACEUTICAL FORMULATION: Polysorbates may also be used as solubilizing agents for a variety of substances including essential oils and oil-soluble vitamins, and as wetting agents in the formulation of oral and parenteral suspensions. They have been found to be useful in improving the oral bioavailability of drug molecules that are substrates for *p*-glycoprotein. Polysorbates are also widely used in cosmetics and food products.

TABLE NO. 19: USES OF POLYSORBATES

Use	Concentration (%)
Emulsifying agent	
Used alone in oil-in-water emulsions	1–15
Used in combination with hydrophilic emulsifiers in oil-in-water emulsions	1–10
Used to increase the water-holding properties of ointments	1–10
Solubilizing agent	
Wetting agent	

DESCRIPTION: Polysorbates have a characteristic odor and a warm, somewhat bitter taste.

TABLE NO. 20: COLORS AND PHYSICAL FORMS OF POLYSORBATES AT 25°C

Polysorbate	Color and form at 25°C
Polysorbate 20	Yellow oily liquid
Polysorbate 40	Yellow oily liquid
Polysorbate 60	Yellow oily liquid
Polysorbate 80	Yellow oily liquid

TYPICAL PROPERTIES:

Solubility:

TABLE NO. 21: SOLUBILITY OF SELECTED POLYSORBATES IN VARIOUS SOLVENTS

Polysorbate	Solvent			
	Ethanol	Mineral oil	Vegetable oil	Water
Polysorbate 20	S	I	I	S
Polysorbate 40	S	I	I	S
Polysorbate 60	S	I	I	S
Polysorbate 80	S	I	I	S

D = dispersible; I = insoluble; S = soluble; T = turbid; W = on warming.

STABILITY AND STORAGE CONDITIONS: Polysorbates are stable to electrolytes and weak acids and bases; gradual saponification occurs with strong acids and bases Polysorbates are hygroscopic and should be examined for water content prior to use and dried if necessary. Polysorbates should be stored in a well-closed container, protected from light, in a cool, dry place.

INCOMPATIBILITIES: Discoloration and/or precipitation occur with various substances, especially phenols, tannins, tars, and tar like

materials. The antimicrobial activity of paraben preservatives is reduced in the presence of polysorbates.

SAFETY: The WHO has set an estimated acceptable daily intake for polysorbates 20, 40, 60, 65, and 80, calculated as total polysorbate esters, at up to 25 mg/kg body-weight. Polysorbate 80: moderately toxic by IV route. Mildly toxic by ingestion, Eye irritation, Experimental tumorigen, reproductive effects, Mutogenic data.

- LD_{50} (mouse, IP): 7.6 g/kg, LD_{50} (mouse, IV): 4.5 g/kg
- LD_{50} (mouse, oral): 25 g/kg, LD_{50} (rat, IP): 6.8 g/kg

HANDLING PRECAUTIONS: Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

LACTOSE MONOHYDRATE

NONPROPRIETARY NAMES

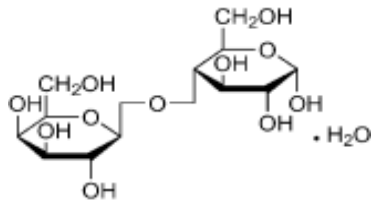
- BP : Lactose monohydrate
- PhEur : Lactosum monohydricum
- JP : Lactose
- USPNF : Lactose monohydrate

SYNONYMS: Aero Flo 20; Aero Flo 65; Aero Flo 95; Anhydrox; CapsuLac; Microfine; Microtose; Pharmatose; PrismaLac; Lactochem; Lactopress; Super – Tab; Zeparox.

CHEMICAL NAME AND CAS REGISTRY NUMBER: O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate [64044-51-5]

EMPIRICAL FORMULA AND MOLECULAR WEIGHT: $C_{12}H_{22}O_{11}\cdot H_2O$ 360.31

STRUCTURAL FORMULA



α-Lactose monohydrate

FUNCTIONAL CATEGORY: Binding Agent; Diluent for dry-powder Inhalers; Tablet Binder; Tablet and Capsule Diluent.

APPLICATIONS IN PHARMACEUTICAL FORMULATION: Lactose is widely used as a filler or diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas. Lactose is also used as a diluent in dry-powder inhalation. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently. Other applications of lactose include use in lyophilized products, where lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose (approximately 1: 3) to prepare sugar-coating solutions.

DESCRIPTION: Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet.

TYPICAL PROPERTIES:

Solubility:

TABLE NO. 22: SOLUBILITY OF LACTOSE

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	Practically insoluble
Ethanol	Practically insoluble
Ether	Practically insoluble
Water	1 in 5.24
	1 in 3.05 at 40°C
	1 in 2.30 at 50°C
	1 in 1.71 at 60°C
	1 in 0.96 at 80°C

SAFETY: Adverse reactions to lactose are largely attributed to lactose intolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase. This results in lactose being undigested and may lead to cramps, diarrhea, distension, and flatulence. The symptoms of lactose intolerance are caused by the osmotic effect of the unabsorbed lactose, which increases water and sodium levels in the lumen. Unabsorbed lactose, upon reaching the colon, can be fermented by colonic flora, which produces gas, causing abdominal distension and discomfort.

In the past, there have been concerns over the transmissible spongiform encephalopathies (TSE) contamination of animal-derived products. However, in the light of current scientific knowledge, and irrespective of geographical origin, milk and milk derivatives are reported as unlikely to present any risk of TSE contamination; TSE risk is negligible if the calf rennet is produced in accordance with regulations.

LD_{50} (rat, IP): >10 g/kg

LD_{50} (rat, oral): >10 g/kg

LD_{50} (rat, SC): >5 g/kg

HANDLING PRECAUTIONS: Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive generation of dust, or inhalation of dust, should be avoided.

COLLOIDAL SILICON DIOXIDE

NONPROPRIETARY NAMES

- BP : Colloidal anhydrous silica
- PhEur : Silica colloidalis anhydrica
- USPNF : Colloidal silicon dioxide

SYNONYMS: Aerosil; Colloidal Silica; Fumed Silica; light Anhydrous Silicic Acid; Silicic Anhydride; Silicon Dioxide fumed;

CHEMICAL NAME AND CAS REGISTRY NUMBER: Silica [7631-86-9]

EMPIRICAL FORMULA AND MOLECULAR WEIGHT: SiO_2 60.08

STRUCTURAL FORMULA: SiO_2

FUNCTIONAL CATEGORY: Adsorbent; Anticaking agent; Emulsion Stabilizer; Glidant; Suspending agent; Tablet Disintegrant; Thermal Stabilizer; Viscosity-Increasing Agent.

APPLICATIONS IN PHARMACEUTICAL FORMULATION: Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations. In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling, and minimize the clogging of spray nozzles. Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders. Colloidal silicon dioxide is frequently added to

suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding, and decrease the release rate. as a thickening agent for topical preparations; and has been used to aid the freeze-drying of nanocapsules and nanosphere suspensions.

TABLE NO. 23: USES OF COLLOIDAL SILICON DIOXIDE

Use	Concentration (%)
Aerosols	0.5–2.0
Emulsion stabilizer	1.0–5.0
Glidant	0.1–0.5
Suspending and thickening agent	2.0–10.0

DESCRIPTION: Colloidal silicon dioxide is submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, nongritty amorphous powder.

TYPICAL PROPERTIES: Solubility: Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.

STABILITY AND STORAGE CONDITIONS: Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. Colloidal silicon dioxide powder should be stored in a well-closed container.

INCOMPATIBILITIES: Incompatible with diethylstilbestrol preparations.

SAFETY: Colloidal silicon dioxide is widely used in oral and topical pharmaceutical products and is generally regarded as an essentially nontoxic and nonirritant excipient. However, intraperitoneal and subcutaneous injection may produce local tissue reactions and/or granulomas. Colloidal silicon dioxide should therefore not be administered parenterally.

LD_{50} (rat, IV): 15 mg/kg, LD_{50} (rat, oral): 3.16 g/kg

HANDLING PRECAUTIONS: Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Precautions should be taken to avoid inhalation of colloidal silicon dioxide. For larger quantities, a dust respirator is recommended.

MAGNESIUM STEARATE

NONPROPRIETARY NAMES

- BP : Magnesium stearate
- JP : Magnesium stearate
- PhEur : Magnesii stearas
- USPNF Magnesium stearate

SYNONYMS: Magnesium Octadecanoate; Octadecanoic Acid, Magnesium Salt; Stearic Acid, Magnesium salt.

CHEMICAL NAME AND CAS REGISTRY NUMBER: Octadecanoic acid magnesium salt [557-04-0].

EMPIRICAL FORMULA AND MOLECULAR WEIGHT: $C_{36}H_{70}MgO_4$ 591.34.

STRUCTURAL FORMULA: $[CH_3 (CH_2)_{16}COO]_2 Mg$.

FUNCTIONAL CATEGORY: Tablet and Capsule Lubricant.

APPLICATIONS IN PHARMACEUTICAL FORMULATION: Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

DESCRIPTION: Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

TYPICAL PROPERTIES: Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

STABILITY AND STORAGE CONDITIONS: Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

INCOMPATIBILITIES: Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

SAFETY: Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation. No toxicity information is available relating to normal routes of occupational exposure. Toxicity assessments of magnesium stearate in rats have indicated that it is not irritating to the skin, and is nontoxic when administered orally or inhaled. Magnesium stearate has not been shown to be carcinogenic when implanted into the bladder of mice.

LD_{50} (rat, inhalation) : >2 mg/L

LD_{50} (rat, oral) : >10 g/kg

HANDLING PRECAUTIONS: Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking. Magnesium stearate should be handled in a well-ventilated environment; a respirator is recommended.

LITERATURE REVIEW

Van Kam *et al*., (1983)[22] studied the crushing strength, disintegration and dissolution properties of tablets, made by wet granulation with lactose as filter, gelatin as binder, potato starch as disintegrant and magnesium stearate as lubricant can be markedly improved when the potato starch (20%) is replaced by a much lower concentration (4%) of an insoluble superdisintegrant, such as sodium starch glycolate (Primogel) or crospovidone (Polyplasdone XL). The incorporation of partially water soluble superdisintegrants such as low-substituted sodium carboxymethylcellulose (Nymcel, ZSD 16), causing a viscous barrier in the tablet disintegration and drug release. In contract to potato starch, the position of the superdisintegrants (intragranular, extragranular or equally distributed) had hardly any effect on the tablet properties. The improved properties of the tablets containing insoluble superdisintegrants, when compared to tablets with potato starch, are the result of the use of much lower concentration of disintegrant, but especially of the difference in effect of magnesium stearate on the disintegration capacity of the slightly swelling potato starch and the strongly swelling superdisintegrants, respectively. The latter cause, even in the presence of the liquid penetration inhibiting hydrophobic magnesium stearate, a chain reaction of opening of the tablet, starting at the outside and resulting in a fast disintegration.

Salom I L *et al*., (1984)[23] Etodolac, a nonsteroidal anti-inflammatory and analgesic drug, was used in a randomized, parallel group, open-label design study, with stool analysis conducted in a blind fashion, to compare its effect in normal men in doses of 400 mg (N = 11) and 600 mg (N = 12) b.i.d. [twice daily] on gastrointestinal microbleeding with that of 600 mg ibuprofen, q.i.d. [4 times a day] (N = 12), 50 mg

Indomethacin in the morning, 50 mg at noon, 100 mg h.s. {N = 9} and 375 mg naproxen b.i.d. (N = 9). Etodolac was given about 2.5 and 3.5 times the mean effective dose used for treating patients with rheumatoid arthritis. The other drugs were given at their manufacturer's maximum recommended doses. Lead-in placebo was given for 1 week, active drug for 1 week and wash out placebo for 1 week. Fetal blood loss was measured by the 51 Cr tragged red cell method, and was averaged over days 4-7 (base line), 11-14 (treatments period) and 17-20 (wash out). The mean increase in blood loss for the treatment period for the 400 mg Etodolac b.i.d. group (0.13 ml) and 600 mg Etodolac b.i.d. (0.10 ml) was significantly less (p = 0.001) than the corresponding valves for Ibuprofen (1.14 ml), Indomethacin (1.20 ml) and Naproxen (0.87 ml). There was no tendency for greater blood loss at higher doses of Etodolac. Etodolac at doses in excess of the mean effective dose in osteoarthritis and rheumatoid arthritis caused significantly less microbleeding in normal male volunteers during the 7-day treatment period than the other drugs, tested and not clinically more than that occurring during baseline placebo.

Gaston G W *et al*., (1986)[24] single oral doses of Etodolac 50, 100 and 200 mg were compared with Aspirin 650 mg in a placebo in a double-blind, parallel group study of 189 out patients reporting moderate or sever pain after oral surgery. Over all efficacies of test drugs was evaluated by sum of pain intensity difference (SPID) source and total pain relief (TOTPAR) scores over 0.5-3, 0.5-6, 0.5-8 and 0.5-12 hours. Etodolac 200 mg provided significantly greater analgesia than Aspirin by these measurements over all SPID and all but one TOPAR interval, and was significantly more effective than placebo over all intervals. Etodolac 100 mg was superior to Aspirin for SPID 0.5-8 and 0.5-12 hours and superior to placebo for both SPID and TOTPAR over all time intervals. Onset of analgesia for Etodolac 100 mg, 200 mg and Aspirin was 1 hour or less for the majority of patients in each group; 42% receiving Etodolac 200

mg reported onset of analgesia within 0.5 hour. Duration of analgesia for Etodolac 200 mg appeared twice that of Aspirin. A significant positive dose-response relationship was obtained for the three doses of Etodolac. A low frequent of side effects was observed in all treatments groups.

Gordon *et al*., (1987)[25] studied the effect of tablet composite solubility and hygroscopicity on the dissolution efficiency of three "superdisintegrants", sodium starch glycolate, crospovidone and croscarmelose sodium, was investigated. Lactose, dicalcium phosphate dehydrate, and sorbitol, alone or in combination, provided varying degrees of solubility and hygroscopicity to the direct compression tablet formulations. To monitor *in vitro* dissolution. 1% p-amino benzoic acid was added to the formulation as a tracer. The results indicate that hygroscopic ingredients decrease the effectiveness of superdisintegrants in promoting *in vitro* dissolution. The greater the overall hygroscopicity of the tablet formulation, the larger the decrease in the efficiency of the superdisintegrant. Composite tablet solubility did not influence the effectiveness of the superdisintegrants. Superdisintegrants that compiled with the same compendia specification, but were manufactured by different companies, behaved similarly in promoting tablet dissolution.

Kraml M *et al*., (1988)[26] the pharmacokinetics of Etodolac have been evaluated in five patients with arthritis given 200 mg Etodolac, twice daily, at 12 hour intervals, for 7 days. Albumin and total protein concentrations were markedly lower in synovial fluid than in serum, and Etodolac free fraction was significantly higher. Etodolac readily penetrated into the synovial fluid, and in the post distributive phase the concentration of free Etodolac (i.e., the drug responsible for pharmacologic activity) remained higher than that in serum at all times. No differences in the half-life of Etodolac elimination were noted.

Sangali *et al*., (1989)[27] studied that the dissolution rate is often the limiting step in gastrointestinal absorption of water insoluble drugs from

solid oral dosage forms. The aim of this work was to use a swellable polymer chosen among superdisintegrants, for improving the dissolution rate of a sparingly soluble drug, loaded on its surface. Nifedipine, which has very low water solubility, was chosen as a model drug, while cross linked sodium carboxymethyl cellulose (Ac-Di-Sol) was chosen as the swellable polymer. The Nifedipine /Ac-Di-Sol systems were prepared using two different techniques: evaporation and spraying; in some preparations polyethylene glycol (PEG 1500), sucrose palmitate (Sucrodent), or dioctyl sodium sulfosuccinate (Aerosal OT) were added. The results of the dissolution tests showed that the dissolution rate of Nifedipine from the systems prepared increase, particularly in the case of the preparation composed of Ac-Di-Sol plus surfactant agents.

Zvaifler N (1989)[28] Etodolac (Lodine, Ramodar, Ultradol), an anti-inflammatory, analgesic agent, is the first of a new class of nonsteroidal anti-inflammatory drugs (NSAIDs), the pyranocarboxylic acids. A review of the literature on numerous clinical studies showed that Etodolac (200 to 600 mg/day) is effective in the treatment of osteoarthritis and rheumatoid arthritis. Etodolac has also been shown to be very well tolerated. In double-blind studies, there were no significant differences in the incidences of new patient complaints except for indigestion between Etodolac-treated groups and placebo-treated groups. Gastrointestinal microbleeding associated with Etodolac was comparable to that with placebo and was significantly less than that associated with other commonly used NSAIDs, such as Ibuprofen, Indomethacin, Piroxicam, and naproxen. The results of laboratory tests, including a detailed analysis of hepatic and renal function, have revealed few abnormalities, most of which were clinically unimportant. When administered to healthy subjects, Etodolac had no pharmacokinetic interactions with three other drugs that are highly bound to serum protein: warfarin, glyburide, and phenytoin.

Brater D C (1990)[29] nonsteroidal anti-inflammatory drugs have been implicated in renal impairment. The purpose of this report is to review the effect of Etodolac, a new anti-inflammatory agent, on renal function and the effect of renal impairment on Etodolac pharmacokinetics. Pharmacokinetics and renal function studies were conducted in normal and in renally impaired volunteers. Additionally, the renal safety of Etodolac was assessed in 2,629 arthritic patients who were treated in clinical trails. The results suggest that Etodolac does not affect renal function in normal individuals, nor does it exacerbate underlying renal insufficient when administered to patients with mild to moderate renal impairment. The pharmacokinetics of Etodolac is unchanged in patients on hemodialysis and in elderly patients. Furthermore, no patient was withdrawn from clinical trails for significantly abnormal renal function test values resulting from Etodolac therapy alone.

Gordon *et al*., (1990)[30] performed a computer-optimized experimental design used to study the effect of incorporating a "superdisintegrant", croscarmelose sodium, intragranularly, extragranularly, or distributed equally between the two phases of a tablet in which a poorly soluble drug constituted at least 92.5% of the formulation. The results were analysed by means of a general quadratic response surface model and suggest that tablets with the same total concentration of superdisintegrant is included intragranularly. Tablet friability was not affected by the method of superdisintegrant incorporation.

Johnson *et al*., (1991)[31] studied the effect of tablet formulation solubility and hygroscopicity on the dissolution efficiency of three "superdisintegrants (sodium starch glycolate, crospovidone, and croscarmelose sodium) in tablets prepared by wet granulation was investigated. Lactose, calcium phosphate dibasic, sorbitol and naproxen sodium, alone or in combination, provided varying degrees of solubility and hygroscopicity in the formulations. To monitor *in vitro* dissolution, 1% of

para-aminobenzoic acid was added to the formulation as a tracer. The results indicate that highly soluble and/or hygroscopic ingredients decrease the effectiveness of superdisintegrants in promoting *in vitro* dissolution. The greater the overall hygroscopicity and solubility of the tablet formulation the larger is the decrease in the efficiency of the superdisintegrant.

Rudraraju *et al*., (1993)[32] investigated the effect of mode of superdisintegrant incorporation in wet granulated tablets with three superdisintegrants: sodium starch glycolate, crospovidone, and croscamelose sodium. This disintegrants were incorporated extragranularly or intragranularly or distributed equally between the two phases. Lactose, naproxen, or dibasic calcium phosphate was used as the principal tablet component to provide various degrees of solubility to the formulations. The formulations were dried to three different levels of moisture content. The results indicated that, for the formulations studied, extragranular incorporation resulted in faster dissolution than did equal distribution intragranularly and extragranularly, which in turn was superior to intragranular incorporation. Granulation moisture content was found to have a formulation-specific impact on tablet dissolution, with each main tablet component behaving in a different fashion. When all other factors were kept constant, there was a tendency for croscarmelose sodium to produce faster tablet dissolution than sodium starch glycolate or crospovidone. The superdisintegrants tended to promote faster dissolution in a neutral pH medium than in an acidic medium

Ahamed *et al*., (1994)[33] studied the influence of various temperature and relative humidity conditions on changes in hardness and friability of five commercial brands of packaged paracetamol tablets stored over a period of six months has been investigated. At 75% of RH all sample show deterioration in harness at 25 degrees (5-10%) and at 45 degrees (10-39%). AT 100% RH there is a -1 little difference in

deterioration in hardness at 25 degree (16-24%) and 45 degree (20-28%) suggesting that once the critical moisture content is reached by the tablets, further increase in relative humidity has little effect on changes in hardness. Under the same conditions, all tablets show an increase in friability ranging from 2.83 to 8.02%. The overall increase in friability with an increase in temperature from 25 degrees to 45 degrees at 75% and 100% RE is 0.0 to 25.2%. The results indicate that moisture sorption by tablet matrix through certain packaging materials may adversely affect the hardness and friability characteristics.

Kichiro Inoue *et al*., (1994)[34] the anti-inflammatory effect of Etodolac (Eto) were compared with those of 6 other anti-inflammatory drugs: Indomethacin (Ind), Diclofenac Na (Dic), Piroxicam (Pir), Naproxen (Nap), Ketoprofen (Ket), and Aspirin (Asp). Eto inhibited carrageenin-induced edema in rats, adjuvant-induced arthritis in rats, acetic acid-induced writhing in mice and brewer's yeast-induced hyperalgesia and fever in rats. In the adjuvant arthritis test, the ED_{30} value (1.88 mg/kg) on day 3 and ED_{50} values (adjuvant-injected paw: 1.18 mg/kg and non-injected paw: 0.96 mg/kg) on day 18 for Eto were comparable to those for Dic (2.16, 1.72 and 1.28) when given prophylactically and the ED_{50} values for Eto (adjuvant-injected paw: 1.61 and non-injected paw: 1.20 mg/kg) were comparable to those for Ket (1.24 and 1.22) when used therapeutically. The analgesic activity of Eto (ED_{50} value: 3.67 mg/kg) in the acetic acid –induced writhing test was greater than that of Nap (9.83) or Asp (31.6) and less than that of Ind (0.71), Dic (1.54), Pir (0.92) or Ket (1.34). In the antipyretic test, the minimum effective dose (MED: 1 mg/kg) for Eto was comparable to that for Ind (1.0), Nap (1.0), Ket (1.0). Eto was less potent in inhibiting carrageenin-induced edema (ED_{30} value: 6.99 mg/kg) and inflammatory pain (ED_{50} value: 9.24mg/kg) than the other drugs (Ind: 2.32 & 3.47, Dic: 0.69 & 3.80, Pir: 1.31 & 1.94, Nap: 1.83 & 2.78, Ket: 1.12 & 0.63), except for Asp (167 & 51.8). Eto was the least

ulcerogenic (UD_{50} value: the dose which cause ulcer action in 50% rats: 84.2 mg/kg) compound among the drugs tested (Ind: 4.24, Dic: 12.7, Pir: 3.14, Nap: 42.3, Ket: 2.69, Asp: 20.8), so its safety margin (the ratio of the UD_{50} value to the $ED_{30,}$ ED_{50} or MED value) was greater than those of the other drug. Thus, Eto is considered to be an effective anti-inflammatory drug with weak ulcerogenic activity.

LJ *et al*., (1996)[35] study the influence of intra and extragranular microcrystalline cellulose (MCC) on drug dissolution from tablets made by high-shear granulation. Granulations were made in a Littleford Model W-10-B (10-liter) mixer and dried in a fluid bed dryer (Niro Inc.) A Plackett Burman Screening design and 2(3) factorial design were employed to study how drug type, MCC (intra-, or extra-), filler type (lactose or dicalcium phosphate), disintegrant type (sodium starch glycolate or croscarmelose sodium) and level, proportion of magnesium stearate, and impeller speed affect tablet hardness, disintegration time, and dissolution. Two model drugs were chosen based on their solubility: metoprolol tartrate (solubility >1000 mg/ml) and hydrochlorothiazide (solubility = 1.05 mg/ml). Tablets were compressed to the same target weight (dose) and similar tablet hardness. In some cases, dissolution testing was also carried out on the loose granules. The intra extragranular distribution of MCC was found critical to the compactability and initial dissolution rates from these tablets. Intragranular MCC reduced drug dissolution, the effect being most marked in the case of the slightly soluble hydrochlorothiazide. For formulations containing intragranular MCC, the granulating fluid level on tablet dissolution was also important, since an increase in fluid level resulted in slower drug dissolution from both the loose granules and the tablets compressed from them. Conversely, extragranular MCC tended to increase both dissolution rates and compactability. It may be concluded that the appropriate distribution of MCC between and within granules may

optimize both dissolution and compactability without changing overall tablet composition.

Rekhi *et al*., (1997)[36] reported the impact of formulation and process changes on dissolution and bioavailability / bioequivalence of metoprolol tartrate immediate release tablets manufactured using a high-shear granulation process. Changes in sodium starch glycolate and magnesium stearate level, and the order of addition microcrystalline cellulose (intra vs. extragranular) were significant only in affecting percent drug release (Q) in 5, 10, and 15 minutes. Statistical analysis of data showed no significant curvature. No examine the impact of formulation and processing variables on *in vivo* absorption, three batches were selected for a bioavailability study based on their dissolution profiles. Subjects received four metoprolol treatments (Lopressor, slow, medium and fast dissolving formulations) separated by I week according to a randomized crossover design. After an overnight fast, subjects were administered one tablet (100 mg), blood samples were collected over 24 hrs and plasma samples were analyzed. The formulations were found to be bioequivalent with respect to the log C_{max} and $\log_{0\text{-}\alpha}$. The results of this study suggest that (i) bioavailability/ bioequivalence studies may not be necessary for metoprolol tartrate immediate release tablet and perhaps other class I drugs after level 2 type changes and (II) *in vitro* dissolution tests may be used to slow bioequivalence of metoprolol formulations with processing or formulation changes within the specified level 2 ranges for the equipment examined.

Chen *et al*., (1998)[37] studied the disintegration and dissolution of acetaminophen tablets containing sucrose and Ac-Di-Sol/Primogel was significantly different between acidic and neutral media. The purpose of this study was to investigate the mechanism of this phenomenon and to propose a way of reducing the dissolution difference between the two media. Tablets of different combinations of active ingredient, sucrose, and Ac-Di-Sol/Primogel were prepared and their dissolution in various media

was evaluated. The dissolution differences were found to be largely related to the hydrophobicity of the active ingredient and pH difference of the two media. This difference was even more evident under the condition where acetaminophen, sucrose, and Primogel were combined. The dissolution difference was therefore attributed to the depressed function of Primogel in the acidic medium, the stronger binding of sucrose, the hydrophobicity of the active ingredient and pH difference of the two media. Increasing the concentration of Primogel or incorporating the surfactant in the tablet can thus greatly decrease the dissolution difference between acidic and neural media.

Richard A. Jones (1999)[38] Etodolac nonsteroidal anti–inflammatory drug (NSAIDs), which has been shown to be effective in the treatment of rheumatoid arthritis and osteoarthritis and a selective COX-2 inhibitor in a wide range of clinically relevant assays in direct comparisons with other NSAIDs. Studies have shown Etodolac to have no overall suppression of gastric or duodenal prostaglandins and endoscopic analysis with Etodolac showed placebo level score in comparison with Ibuprofen, which showed inducement of gastro-intestinal (GI) side effects. This high degree of gastric tolerability was further demonstrated by microbleeding studies. The favorable GI tolerability profile of Etodolac has been shown in long-term and large-scale trails and by routine clinical observation. In summary, Etodolac is a well established selective COX-2 inhibitor that has been shown not to suppress gastric or duodenal prostaglandins, to have minimal hepatic or renal effects and to have favorable GI tolerability in comparison with Ibuprofen

Lopex-Solis *et al*., (2001)[39] studied the effect of disintegrant hygroscopicity on dissolution of tablets obtained by compression at 85 MPa of mixtures of Norfloxacin and different proportions of a disintegrant (starch 1500, PVP XL 10 or Croscarmelose sodium) and a diluents (Pharmatose DCL 11). Dissolution behavior was evaluated according to

USP23, apparatus 2 (paddle) at 50 rpm and using 750 ml acetate buffer solution of pH 4, at 37 degrees C, as medium. Norfloxacin added of increasing proportions, in a given range, of each disintegrant or the diluents increased the drug dissolved. Addition of increasing proportions of pharmatose DCL 11 to Norfloxacin with 5% of the high hygroscopic starch 1500 reduced the dissolution improvement effect of pharmatose DCL 11. Addition of 5% pharmatose DCL 11 to tablets of the middle hygroscopic Croscarmelose sodium and Norfloxacin slightly reduced the croscarmelose sodium dissolution promoting effect, while addition of 15% pharmatose DCL 11 to tablets of the low hygroscopic PVP XL 10 and Norfloxacin showed no inhibition but potentiated substantially the dissolution of Norfloxacin. These effects were attributed to competition for the available water in the tablet and to different water consume, for dissolution or hydration, by the diluents and the disintegrants.

L.H.Reddy *et al*., (2002)[40] recently, fast-dissolving drug delivery systems have started gaining popularity and acceptance as a new drug delivery systems, because they are easy to administer and lead to better patient compliance. Usually, elderly people experience difficulty in swallowing the conventional dosage forms because of tremors of extremities and dysphagia. Fast-dissolving drug delivery systems may offer a solution for these problems. Fast-dissolving drug delivery systems can be achieved by various techniques like direct compression, wet granulation, compression moulding, volatization and freeze-drying. They involve different mechanisms like use of high amounts of hydrophilic disintegrating agents of effervescent combinations, which allow the dosage forms to disintegrate quickly in the patient's mouth on constant with saliva. There are more than fifteen fast-dissolving products in the market worldwide.

Shenoy *et al*., (2003)[41] prepared the fast dissolving tablets of diclofenac sodium using direct compression after incorporating

superdisintegrants such as cross linked carboxymethylcellulose, sodium starch glycolate and cross linked povidone in different concentrations. All the formulations were evaluated for the influence of disintegrants and their concentrations on the characteristics of fast dissolving tablet mainly in terms of disintegration time and dissolution rate. Tablets containing cross-linked carboxymethylcellulose showed better disintegrating character along with rapid release (90 percent drug release in 10 min). No appreciable difference was found between the formulations containing other two superdisintegrants. The concentration of the superdisintegrants had also an effect on disintegration time and *in vitro* dissolution. There seems to be a trend towards use of higher level of disintegrants producing rapid disintegration and faster dissolution. The resulting tablets were also evaluated for its hardness and friability and were found to be independent of disintegrant concentration.

Nayak S. M *et al*., (2004)[42] the present study is about a tablet, which can disintegrate or dissolve rapidly once placed into the oral cavity. Fast dissolving tablets of promethazine thecolate were prepared using effervescent melt, superdisintegrant addition and melt technologies. All the prepared formulations were evaluated for various granule and tablet characteristics. Significant rapid release of drug from the formulated tablets was observed in comparison to the control tablets. Tablets from effervescent melt and superdisintegrant addition technique release 92% and 89% of the drug at the end of 10 minutes respectively. Study concluded fast dissolving tablets of promethazine theoclate could be prepared successfully. Tablets with added patient benefits and increased consumer satisfaction.

Stephen L. *et al*., (2005)[43] the increasing use of nonsteroidal anti-inflammatory drugs (NSAIDs) in small animals has resulted in the development of new and innovative additions to this class of drugs. Examples of NSAIDs now available for use in small animals include

aspirin, Etodolac, Carprofen, Ketoprofen, Meloxicam, Deracoxib, and Tepoxalin. The purposes of this article are to review the pathophysiology of prostaglandin synthesis and inhibition, the mechanisms of action, pharmacokinetics, pharmacological effects, and potential adverse reactions of aspirin and the newly released NSAIDs.

Souliman S *et al*., (2006)[44] the first purpose of this study was to simulate the impact of food intake on drug release and absorption *in vivo* using a novel *in vitro* system which mimics the gastro-intestinal (GI) tract in man. The drug studied was acetaminophen in the form of immediate release (IR) tablets. The second purpose was to establish a level an *in vitro* / *in vivo* correlation that could predict the bioavailability of a drug instead of using difficult, time-consuming and expensive *in vivo* bioequivalence studies. The artificial digestive system was used to estimate the availability of acetaminophen IR tablets for absorption in fasted and fed states. The same study was performed *in vivo* under similar conditions. A comparison study was carried out between the classical and the novel methods to estimate the efficacy of the new *in vitro* system to simulate the influence of food on drug release and absorption *in vivo*. A level A *in vitro* / *in vivo* correlation was established with a correlation coefficient of 0.9128 and 0.9984 in the fasted and fed states, respectively. Compared to USP II method, the novel *in vitro* model demonstrated a high level of efficacy in mimicking the behavior of acetaminophen IR tablets *in vivo* in fasted and fed states.

Manzo RH *et al*., (2006)[45] Literature data relevant to the decision to allow a waiver of *in vivo* bioequivalence (BE) testing for the approval of immediate release (IR) solid oral dosage forms containing Amitriptyline hydrochloride are reviewed. Its therapeutic uses, its pharmacokinetic properties, the possibility of excipient interactions and reported BE/bioavailability (BA) problems are also taken into consideration. Literature data indicates that amitriptyline hydrochloride is a highly

permeable active pharmaceutical ingredient (API). Data on the solubility according to the current Biopharmaceutics Classification System (BCS) were not fully available and consequently amitriptyline hydrochloride could not be definitively assigned to either BCS Class I or BCS Class II. But all evidence taken together, a biowaiver can currently be recommended provided that IR tablets are formulated with excipients used in existing approved products and that the dissolution meets the criteria defined in the Guidances. (c) 2006 Wiley-Liss, Inc. and the American Pharmacists Association

Dukić-Ott A, ***et al*., (2007)**[46] the aim of this study was to evaluate modified starch (high-amylose, crystalline and resistant starch) as the main excipient for immediate-release pellets containing poorly soluble drugs (hydrochlorothiazide and piroxicam) and prepared via extrusion / spheronisation. The bioavailability of pellets (containing 50 mg hydrochlorothiazide) was determined after oral administration to 6 dogs. A 2(4)-factorial design with central point was used to evaluate the influence of hydrochlorothiazide (10% and 50%, w/w), HPMC (binder, 4% and 7%, w/w), sorbitol (0% and 10%, w/w) and water (granulation liquid, low and high level) on pellet yield, size (Feret mean diameter) and sphericity (aspect ratio and two-dimensional shape factor). Optimal granulation liquid content depended on drug and sorbitol level in the formulation. All factors except sorbitol content, as well as the interactions between drug concentration and binder level and between drug and water level, were significant ($P<0.05$) for pellet yield, while a significant curvature ($P<0.05$) suggested non-linearity of the response plots. The model was not significant for pellet shape, while hydrochlorothiazide and water level as well as their interaction were significant ($P<0.05$) for pellet size. Pellet friability, disintegration, residual water content and in-vitro drug release were determined. Pellets containing 2.5% (w/w) piroxicam were also evaluated. For both model drugs, pellets with a high yield (>90%),

acceptable sphericity (AR<1.2) and low friability (<0.01%) were obtained. Due to pellet disintegration, fast dissolution of both hydrochlorothiazide and piroxicam was achieved: >80% drug released in 30 min. The bioavailability ($AUC_{0>24\ h}$, C_{max} and t_{max}) of hydrochlorothiazide pellets in dogs was not significantly different from fast-disintegrating immediate-release hydrochlorothiazide tablets (P>0.05).

El-Barghouthi M, ***et al*.**, **(2008)**[47] Disintegrants and fillers represent important excipients for immediate-release solid dosage forms in many pharmaceutical applications. A new excipient based on the coprecipitation of chitosan and silica has been achieved. The "intimate" physical association between chitosan and silica creates an insoluble, hydrophilic, highly absorbent material, consequently, resulting in superiority in water uptake, water saturation for gelling formation, and compactability among other superdisintegrants. The new excipient has an outstanding functionality that does not primarily depend on water wicking and swelling properties. In fact, it translates it into superior disintegration characteristics with improved powder flow and compaction properties. Thus, the new excipient could act as a superdisintegrant and pharmaceutical filler at the same time. Studies have shown that chitosan-silica delivers superior performance in wet granulation formulations and is the only disintegrant that is effective at all concentrations in tablet formulation.

Sekar V, **Chellan VR (2008)**[48] Telmisartan (anti-hypertensive) is insoluble in water; hence the drug may be slowly or incompletely dissolved in the gastro intestinal tract. So the rate of dissolution and therefore its bioavailability is less (bioavailability 42%). In the present study an attempt has been made to prepare immediate release tablets of telmisartan by using Polyplasdone XL-10 (crospovidone) at intragranular, extragranular and partly intra and extragranular level of addition to increase the rate of drug release from dosage form to increase the dissolution rate and hence its bioavailability. The prepared granules and tablets were evaluated for

their physiochemical properties and in-vitro dissolution study was conducted for the prepared tablets. It was concluded that the immediate release tablets with proper hardness, disintegration time and with increase rate of dissolution can be made using Polyplasdone XL-10. Formulation-10 (F10) was selected for stability study and the in-vitro dissolution study showed that was no difference in percent of drug released between initial and sixth month sample.

TABLE NO. 24: EQUIPMENTS USED FOR TABLET FORMULATION

Name of equipment	Name of company
Tablet punching machine	Rimek Mini Press 1
Tablet disintegration test apparatus	Remi equipments
Pfizer tablet hardness tester	Scientific Engineering Corporation
Roche friability tester	Remi equipments
Dissolution apparatus	Lab India Disso 2000
UV spectrophotometer	Jasco V 530
FT IR spectrophotometer	(Jasco-FT-IR 8201 PC)
pH tester 1 (water proof)	Oakton instruments.
Electronic Balance	Alpha Innotech Corporation

TABLE NO. 25: MATERIALS USED FOR TABLET FORMULATION

Name of the materials	Name of company
Etodolac	Dr. Reddy's Laboratories, Hyderabad.
Lactose	SD Fine chemicals Ltd, Mumbai.
Micro crystalline cellulose	SD Fine chemicals Ltd, Mumbai.
Crospovidone	Aurobindo Pharmaceutical, Hyderabad.
Sodium Starch Glycolate	Aurobindo Pharmaceutical, Hyderabad.
Magnesium stearate	SD Fine chemicals Ltd, Mumbai.
Povidone	SD Fine chemicals Ltd, Mumbai.
Colloidal Silicon dioxide	SD Fine chemicals Ltd, Mumbai.
Polysorbate 80	SD Fine chemicals Ltd, Mumbai.

ANALYTICAL METHODS

METHODS AVAILABLE FOR THE IDENTIFICATION OF ETODOLAC ARE[48]

a) Examine by infrared absorption spectrophotometry, comparing with the spectrum obtained with the spectrum obtained with Etodolac
b) Melting point: 144°C to 150°C.
c) The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

METHODS AVAILABLE FOR ESTIMATION OF ETODOLAC ARE

a) Spectrophotometric estimation of Etodolac in pure form and pharmaceutical formulation was reported.[49]
b) Spectrofluorimetric determination of Etodolac was reported. The detection limit was reported to be 96 to 640 ng/ml.[50]
c) The separation of Etodolac and its metabolites has been reported by the use of Capillary electro – chromatography.[2]
d) HPLC and Mass spectrometry was reported for the determination of Etodolac in human plasma.[51]

METHOD FOR ESTIMATION OF ETODOLAC

A spectrophotometric method based on the measurement of absorbance at 274 nm in 0.1 M phosphate buffer pH 6.8 was used in the present study for estimation of Etodolac.

MATERIALS

1. Etodolac pure drug.
2. Methanol.

3. Potassium dihydrogen phosphate.
4. Sodium hydroxide
5. Distilled water.

THE METHODOLOGY USED IN THE PRESENT RESEARCH WORK[52]

Preparation of pH 6.8 phosphate buffer:

250 ml of 0.2M potassium dihydrogen phosphate in a 100 ml vessel and 112 ml of 0.2 M NaOH and made up to 1000 ml with water.

Potassium dihydrogen phosphate (0.2M)

Dissolve 27.218 g of potassium dihydrogen phosphate in water and dilute to 1000 ml with water.

Sodium hydroxide (0.2M) NaOH

Dissolve 8 g of NaoH in water and dilute to 1000 ml with water.

Preparation of standard stock solution

100 mg of Etodolac pure drug was dissolved in 2-4 ml of methanol in a 100 ml of volumetric flask and the solution was made up to the mark with phosphate buffer pH 6.8.

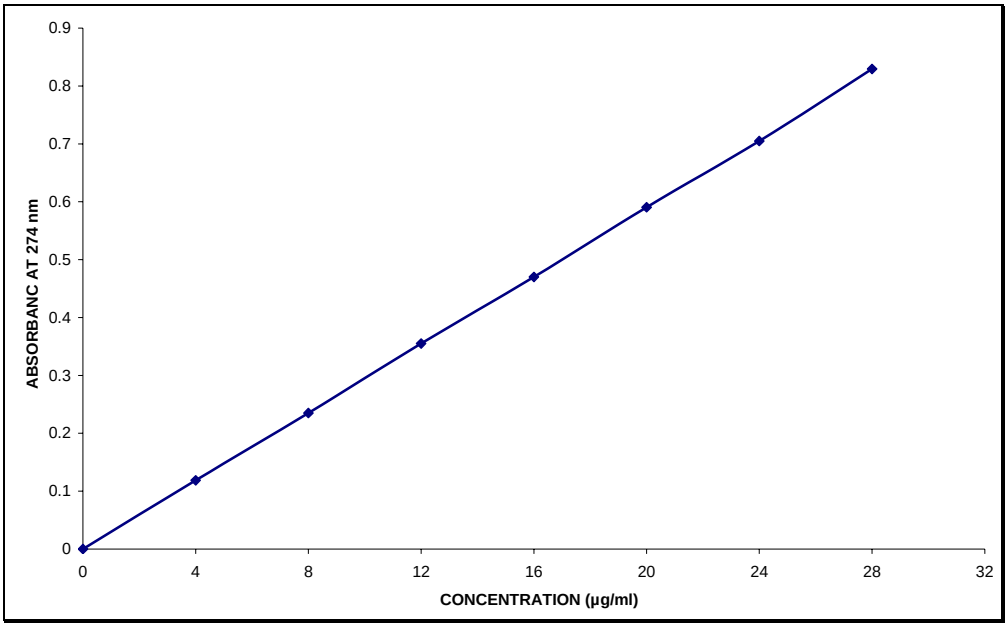
Procedure for standard graph

The standard solution of Etodolac was subsequently diluted with 0.1 M, pH 6.8 phosphate buffer to obtain a series of dilutions containing 4 µg/ml, 8, 12, 16, 20, 24, 28 µg/ml of Etodolac in 1 ml solution. The absorbance of these solutions was measured in Shimadzu UV-1600 UV- visible spectrophotometer using 0.1M, pH 6.8 phosphate buffer as blank. The concentration of Etodolac used and the corresponding absorbances were given in table no. 26 and the absorbance was plotted against different concentrations of Etodolac as shown in Figure No. 7.

TABLE NO. 26: STANDARD GRAPH VALUES OF ETODOLAC IN 0.1M, PH 6.8 PHOSPHATE BUFFER

Concentration µg/ml	Absorbance at 274 nm
4	0.1187
8	0.2350
12	0.3550
16	0.4701
20	0.5906
24	0.7050
28	0.8295

FIGURE NO. 7: STANDARD GRAPH OF ETODOLAC IN 0.1M, pH 6.8 PHOSPHATE BUFFER



FORMULATION OF ETODOLAC IMMEDIATE RELEASE TABLETS

Etodolac, is a Non Steroidal Anti-Inflammatory Drug (NSAID), of the pyranocarboxylic acid class. Etodolac is a synthesized anti-inflammatory drug with potent inhibitory activity against interleukin-1 beta (IL-1beta)-induced prostaglandin E2 biosynthesis in chondrocytes. Etodolac, is water insoluble drug and soluble in methanol, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol. The ten different batches of Etodolac immediate release tablets were formulated by wet granulation method using two different superdisintegrants such as crospovidone (polyplasdone XL-10) and sodium starch glycolate in three different ratios (2%, 4%, 6%) by intra, extra and partly intra and extragranular addition method.

INGREDIENTS

TABLE NO. 27: INGREDIENTS FOR ETODOLAC IMMEDIATE RELEASE TABLETS

Drug	Etodolac, a nonsteroidal anti-inflammatory.
Diluent	Lactose monohydrate used as fillers (LMH).
Disintegrant	Microcrystalline cellulose (MCC).
Superdisintegrants	Crospovidone and Sodium Starch Glycolate help to dispersing the drug particle and used to increase the rate of drug release.
Wetting agent / Solubilizer	Polysorbate80 used to enhance disintegration and dissolution of Etodolac
Binder	Povidone (PVP) used for formation of granules.
Glidant	Colloidal silicon dioxide used as glidant
Lubricant	Magnesium stearate improves the rate of flow of tablet granules.

Chapter 8 Formulation of Etodolac IR Tablets

PREPARATION OF ETODOLAC IMMEDIATE RELEASE TABLETS

The ten different batches of Etodolac immediate release tablets were prepared and formulated by Wet Granulation method. And it involve the following procedure –

PROCEDURE FOR FORMULATION OF ETODOLAC CONVENTIONAL TABLETS (F1) WITHOUT ADDING SUPERDISINTEGRANTS

***Step 1*:** Weigh all ingredients as per formula.

Step 2: Sift LMH and MCC through sieve no. 40.

***Step 3*:** Mix step 2 powders with drug then pass through sieve no. 30. Mix the above powder for 15 minutes in a poly bag.

***Step 4*:** (Preparation of binder): Mix PVP with required quantity of water, then stirrer the solution until PVP dissolved completely, in that add polysorbate80 and mix well. Then immediately mix with step 3 powders to form granules.

***Step 5*:** (Drying): Keep the formed granules for air drying, after drying; pass the granules through 20 mesh to get uniform granules.

Step 6: Sift magnesium stearate through sieve no. 40, mix it with colloidal silicon dioxide and step 5 granules for 2 minutes in a poly bag.

***Step 7*:** Now the blend (step 6) is compressed for target weight 490 mg using 12 mm flat punch.

PROCEDURE FOR FORMULATION OF ETODOLAC IMMEDIATE RELEASE TABLETS WITH SUPERDISINTEGRANTS BY INTRAGRANULAR ADDITION METHOD (F2, F3 AND F4).

Step 1: Weigh all ingredients as per formula.

***Step 2*:** [Intragranular (before granulation)]: Sift LMH, MCC and crospovidone and sodium starch glycolate through sieve no. 40.

Step 3: Mix step 2 powders with drug then pass through sieve no. 30. Mix the above powder for 15 minutes in a poly bag.

Step 4: (Preparation of binder): Mix PVP with required quantity of water, then stirrer the solution until PVP dissolved completely, in that add polysorbate80 and mix well. Then immediately mix with step 3 powders to form granules.

Step 5**:** (Drying): Keep the formed granules for air drying, after drying; pass the granules through 20 mesh to get uniform granules.

Step 6**:** Sift magnesium stearate through sieve no. 40, mix it with colloidal silicon dioxide and step 5 granules for 2 minutes in a poly bag.

Step 7*:* Now the blend (step 6) is compressed for target weight 490 mg using 12 mm flat punch.

PROCEDURE FOR FORMULATION OF ETODOLAC IMMEDIATE RELEASE TABLETS WITH SUPERDISINTEGRANTS BY EXTRAGRANULAR ADDITION METHOD (F5, F6 AND F7).

Step 1: Weigh all ingredients as per formula.

Step 2: Sift LMH and MCC through sieve no. 40.

Step 3**:** Mix step 2 powders with drug then pass through sieve no. 30. Mix the above powder for 15 minutes in a poly bag.

Step 4**:** (Preparation of binder): Mix PVP with required quantity of water, then stirrer the solution until PVP dissolved completely, in that add polysorbate80 and mix well. Then immediately mix with step 3 powders to form granules.

Step 5: (Drying): Keep the formed granules for air drying, after drying, pass the granules through 20 mesh to get uniform granules.

Step 6: [Extragranular (After granulation)] Sift crospovidone and sodium starch glycolate, magnesium stearate through sieve no. 40, mix it with colloidal silicon dioxide and step 5 granules for 2 minutes in a poly bag.

Step 7: Now the blend (step 6) is compressed for target weight 490 mg using 12 mm flat punch.

PROCEDURE FOR FORMULATION OF ETODOLAC IMMEDIATE RELEASE TABLETS WITH SUPERDISINTEGRANTS BY INTRA-EXTRAGRANULAR ADDITION METHOD (F8, F9 AND F10).

***Step 1*:** Weigh all ingredients as per formula.

***Step 2*:** [Intragranular (before granulation)]: Sift LMH, MCC and crospovidone (polyplasdone XL-10), sodium starch glycolate through sieve no. 40.

Step 3: Mix step 2 powders with drug then pass through sieve no. 30. Mix the above powder for 15 minutes in a poly bag.

***Step 4*:** (Preparation of binder): Mix PVP with required quantity of water, then stirrer the solution until PVP dissolved completely, in that add polysorbate80 and mix well. Then immediately mix with step 3 powders to form granules.

Step 5: (Drying): Keep the formed granules for air drying, after drying, pass the granules through 20 mesh to get uniform granules.

***Step 6*:** [Extragranular (After granulation)] Sift crospovidone and sodium starch glycolate, magnesium stearate through sieve no. 40, mix it with colloidal silicon dioxide and step 5 granules for 2 minutes in a poly bag.

Step 7: Now the blend (step 6) is compressed for target weight 490 mg using 12 mm flat punch.

TABLE NO. 28: FORMULA OF ETODOLAC IMMEDIATE RELEASE TABLETS CONTAINING CROSPOVIDONE AND SODIUM STARCH GLYCOLATE BY "INTRAGRANULAR ADDITION METHOD" AT DIFFERENT CONCENTRATION (2%, 4% AND 6%) AND CONTROL TABLETS (F1)

S. No	Ingredients	Quantity / Unit Dose (mg)			
		F1	F2	F3	F4
1.	Etodolac	300	300	300	300
2.	Lactose monohydrate	98 (20%)	78.5 (15%)	58.8 (12%)	39.2 (8%)
3.	Microcrystalline cellulose (12.2%)	60	60	60	60
4.	Crospovidone,	-	9.8 (2%)	19.6 (4%)	29.4 (6%)
5.	Sodium starch glycolate	-	9.8 (2%)	19.6 (4%)	29.4 (6%)
6.	Povidone (3%)	14.7	14.7	14.7	14.7
7.	Polysorbate 80 (1%)	4.9	4.9	4.9	4.9
8.	Colloidal silicon dioxide (1%)	4.9	4.9	4.9	4.9
9.	Magnesium stearate (1.5%)	7.35	7.35	7.35	7.35
10.	Target weight of Etodolac IR tablet	490	490	490	490

TABLE NO. 29: FORMULA OF ETODOLAC IMMEDIATE RELEASE TABLETS CONTAINING CROSPOVIDONE AND SODIUM STARCH GLYCOLATE BY "EXTRAGRANULAR ADDITION" METHOD AT DIFFERENT CONCENTRATION (2%, 4% AND 6%)

S. No.	Ingredients	Quantity / Unit Dose (mg)		
		F5	F6	F7
1.	Etodolac	300	300	300
2.	Lactose monohydrate	78.5 (15%)	58.8 (12%)	39.2 (8%)
3.	Microcrystalline cellulose (12.2%)	60	60	60
4.	Crospovidone	9.8 (2%)	19.6 (4%)	29.4 (6%)
5.	Sodium starch glycolate	9.8 (2%)	19.6 (4%)	29.4 (6%)
6.	Povidone (3%)	14.7	14.7	14.7
7.	Polysorbate 80 (1%)	4.9	4.9	4.9
8.	Colloidal silicon dioxide (1%)	4.9	4.9	4.9
9.	Magnesium stearate (1.5%)	7.35	7.35	7.35
10.	Target weight of Etodolac IR tablet	490	490	490

TABLE NO. 30: FORMULA OF ETODOLAC IMMEDIATE RELEASE TABLETS CONTAINING CROSPOVIDONE AND SODIUM STARCH GLYCOLATE BY "INTRA AND EXTRAGRANULAR ADDITION METHOD" AT DIFFERENT CONCENTRATION (2%, 4% AND 6%)

S. No.	Ingredients	Quantity / Unit Dose (mg)		
		F8	F9	F10
1.	Etodolac	300	300	300
2.	Lactose monohydrate	78.4	58.8	39.2
3.	Microcrystalline cellulose (12.2%)	60	60	60
4.	Crospovidone,	9.8 (2%)	19.6 (4%)	29.4 (6%)
5.	Sodium starch glycolate	9.8 (2%)	19.6 (4%)	29.4 (6%)
6.	Povidone (3%)	14.7	14.7	14.7
7.	Polysorbate 80 (1%)	4.9	4.9	4.9
8.	Colloidal silicon dioxide (1%)	4.9	4.9	4.9
9.	Magnesium stearate (1.5%)	7.35	7.35	7.35
10.	Target weight of Etodolac IR tablet	490	490	490

TABLE NO. 31: CONCENTRATION OF SUPERDISINTEGRANTS (CROSPOVIDONE AND SODIUM STARCH GLYCOLATE) IN ALL FORMULATION

S. No.	Formulation code	Superdisintegrants (Crospovidone (polyplasdone XL-10), Sodium Starch Glycolate)			
		Intragranular		Extragranular	
		Amount (%)	Concentration (Mg)	Amount (%)	Concentration (Mg)
1.	F1(Control)	-	-	-	-
2.	F2	2	9.8	-	-
3.	F3	4	19.6	-	-
4.	F4	6	29.4	-	-
5.	F5	-	-	2	9.8
6.	F6	-	-	4	19.6
7.	F7	-	-	6	29.4
		Intra and Extragranular			
8.	F8	1	4.9	1	4.9
9.	F9	2	9.8	2	9.8
10.	F10	3	14.7	3	14.7

EVALUATION OF POWDERED BLEND

EVALUATION OF POWDERED BLEND

Blend means a mixture of pure drug (Etodolac) and other excipients which was used in formulation. The prepared blend was evaluated for the following tests and the results were given in the table no. 32.

- Angle of repose
- Bulk density
- Tapped density
- Carr's index / % compressibility index
- Hausner's ratio

ANGLE OF REPOSE FOR PURE ETODOLAC DRUG POWDER

First a funnel was fixed at a particular height 'h' cm on a burette stand. A white paper was placed below the funnel on the table. The Etodolac powder drug whose angle of repose was to be determined was passed slowly through the funnel, until it forms a pile. Further addition of Etodolac powder was stopped as soon as the Etodolac powder pile touches the tip of the funnel. Circumferences of the pile of drug are drawn with a pencil without disturbing the pile. The radius of the pile was noted down as 'r' cm angle of repose θ^0 of Etodolac pure drug was calculated by using the formula, and results are given in table no. 32.

$$\theta = tan^{-1}\left(\frac{h}{r}\right)$$

where h = height of the pile

r = radius of the pile

BULK DENSITY FOR PURE ETODOLAC DRUG POWDER

Weighed and take 5 gm of pure Etodolac drug powder in measuring cylinder and calculate bulk density.

$$\text{Bulk density} = \frac{M}{V_0}$$

where M = weight of active ingredient in grams

V_o = unsettled apparent volume in cm^3

The unsettled apparent volume of pure drug of Etodolac in measuring cylinder was measured by normal scale. And the results are given in table no. 32.

TAPPED DENSITY FOR PURE ETODOLAC DRUG POWDER

Weighed and take 5 gm of pure Etodolac drug powder in measuring cylinder. Tap it gently on a wooden surface from a height of 1 inch for 100 times and calculate tapped density. And the results are given in table no. 32.

$$\text{Tapped density} = \frac{M}{Vf}$$

where M = weight of API,

V_f = tapped volume

COMPRESSIBILITY INDEX FOR PURE ETODOLAC DRUG POWDER

Compressibility index of pure Etodolac drug powder was calculated by following formula and results are given in table no. 32.

$$\text{Compressibility Index} = 100 \times \left(\frac{\rho_{tapped} - \rho_{Bulk}}{\rho_{tapped}} \right)$$

where ρ_{tapped} = tapped density

ρ_{Bulk} = bulk density

HAUSNER'S RATIO FOR PURE ETODOLAC DRUG POWDER

Hausner's ratio of pure Etodolac drug powder was calculated by following formula and results are given in table no. 32.

$$\text{Hauser ratio} = \left(\frac{\rho_{tapped}}{\rho_{Bulk}} \right)$$

ANGLE OF REPOSE FOR PURE ETODOLAC DRUG POWDER AND WITH OTHER EXCIPIENTS

First a funnel was fixed at a particular height 'h' cm on a burette stand. A white paper was placed below the funnel on the table. The Etodolac powder drug and with other excipients powder whose angle of repose was to be determined was passed slowly through the funnel, until it forms a pile. Further addition of Etodolac powder and other excipients powder was stopped as soon as the mixture of Etodolac drug powder and other excipients powder, pile touches the tip of the funnel. Circumferences of the pile of drug are drawn with a pencil without disturbing the pile. The radius of the pile was noted down as 'r' cm angle of repose θ^0 of a mixture of Etodolac pure drug powder and other excipients powder and was calculated by using the formula, and results are given in table no. 32.

BULK DENSITY FOR PURE ETODOLAC DRUG POWDER AND WITH OTHER EXCIPIENTS

Weighed and take 3 gm of pure Etodolac drug powder and with other excipients powder and mix it and pour in a measuring cylinder and calculate bulk density. The results are given in table no. 32.

Chapter 9 Evaluation of Powdered Blend

TAPPED DENSITY FOR PURE ETODOLAC DRUG POWDER AND WITH OTHER EXCIPIENTS

Weighed and take 3 gm of pure Etodolac drug powder and with other excipients powder and mix it and pour in a measuring cylinder and calculate tapped density. The results are given in table no. 32.

COMPRESSIBILITY INDEX FOR PURE ETODOLAC DRUG POWDER AND WITH OTHER EXCIPIENTS

Compressibility index of pure Etodolac drug powder and with other excipients powder was calculated by following formula and results are given in table no. 32.

HAUSNER'S RATIO FOR PURE ETODOLAC DRUG POWDER AND WITH OTHER EXCIPIENTS

Hausner's ratio of pure Etodolac drug powder and with other excipients powder was calculated by following formula and results are given in table no. 32.

TABLE NO. 32: ANGLE OF REPOSE, BULK DENSITY, TAPPED DENSITY, COMPRESSIBILITY INDEX, HAUSNER'S RATIO OF ETODOLAC PURE DRUG AND FORMULATED ETODOLAC IR TABLETS (F1, F2, F3, F4, F5, F6, F7, F8, F9 AND F10)

S. No.	Properties	Pure drug	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Angle of repose (θ)	35.47 ± 1.09	26.58 ± 0.35	27.39 ± 0.32	27.39 ± 0.32	27.39 ± 0.32	26.41 ± 0.72	26.41 ± 0.72	26.41 ± 0.72	25.89 ± 0.55	25.89 ± 0.55	25.89 ± 0.55
2.	Bulk density (gm/cm^3)	0.33	0.69	0.73	0.73	0.73	0.74	0.74	0.74	0.75	0.75	0.75
3.	Tapped density (gm/cm^3)	0.41	0.78	0.81	0.81	0.81	0.82	0.82	0.82	0.83	0.8.3	0.83
4.	Carr's index (%)	40	7.5	7.5	7.5	7.5	7.4	7.4	7.4	7.2	7.2	7.2
5.	Hausner ratio	1.6	1.08	1.08	1.08	1.08	1.08	1.08	1.08	1.07	1.07	1.07
6.	Flow property	Very poor	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent

EVALUATION TESTS FOR ETODOLAC IR TABLETS

The formulated Etodolac IR tablets were evaluated for the following tests:

1. General appearance:
   a) Organoleptic properties (color, odor and taste)
   b) Size and shape (thickness and diameter)
2. Mechanical Strength of tablets:
   a) Hardness or Crushing strength
   b) Friability
3. Weight variation
4. Assay preparation
5. Content Uniformity
6. Disintegration
7. Dissolution
8. Compatibility studies
   - TLC
   - IR

GENERAL APPEARANCE

The general appearance of tablets, its visual identity and overall 'elegance' is essential for consumer acceptance for monitoring the production process. The control of general appearance involves measurement of attributes such as a tablet's size, shape, color, presence or absence of odour, taste, surface textures, physical flaws and consistency.

Chapter 10 Evaluation of Etodolac IR Tablets

ORGANOLEPTIC PROPERTIES

Color is a vital means of identification. Reflectance Spectrophotometry, Tristimulus Colorimetric Measurements and Micro Reflectance Photometer have been used to measure color uniformity and gloss on a tablet surface. In preparation of Etodolac IR tablets no coloring agents were added. And the color of the Etodolac IR tablets was in off-white.

Odor may also be important for consumer acceptance of tablets and can provide an indication of the quality of tablets. No odor was observed in Etodolac IR tablets.

Taste is also important for consumer acceptance of tablets. The taste of Etodolac IR tablets was checked.

TABLET SIZE AND SHAPE

The shape and dimensions of compressed tablets are determined by the type of tooling during the compression process.

TABLET THICKNESS

Tablets thickness varies with changes in die fill, particle size distribution and packing of the powder mix being compressed. The thickness of individual tablet of Etodolac IR tablets was measured with a Micrometer. Tablet thickness should be controlled within a ±5% variation of a standard value. At frequent time interval, from each batch 5 Etodolac IR tablets was taken and mean of 5 tablets was calculated and the results was given in the table no. 33.

TABLET DIAMETER

The diameter of the Etodolac IR tablets was checked with Vernier calipers. At frequent time interval, from each batch 5 tablets was taken and

mean of 5 tablets was calculated and the results was given in the table no. 33.

MECHANICAL STRENGTH OF TABLETS

The mechanical strength of a tablet provides a measure of the bonding potential of the material concerned and this information is useful in the selection of excipients.

HARDNESS OR CRUSHING STRENGTH

It is usually measured by the use of the Monsanto, Pfizer and Schleuniger. The resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage depend on its results are given in table no. 34.

FRIABILITY TEST

Friability test is usually measured by the use of the Roche Friabilator. Ten Etodolac IR tablets from each batch were weighed (W_o) initially and placed in a rotating drum. Then, they were subjected to 100 revolutions. After completion of 100 revolutions or 4 minutes of time, the tablets were again weighed (W). The friability or loss in weight (f) was calculated by the formula given

$$f = \left[1 - \frac{W}{W_O}\right] \times 100$$

A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up. And results are given in table no. 34.

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WEIGHT VARIATION

For uniformity of weight, twenty tablets from each batch of formulated Etodolac IR tablets were selected at random. The individual and total weight of 20 tablets from each batch was determined.

The results are given in table no. 34. Limit: Not more than two of the tablets must differ from the average weight by not more than the percentages. No tablet must differ by more than double the relevant percentage.

CONTENT UNIFORMITY

For content uniformity test, representative samples of 30 tablets are selected and 10 are assayed individually. From each batch of formulated Etodolac IR tablets, ten tablets weighed and powdered. The powdered sample equivalent to Etodolac 50 mg was weighed and then taken in a stoppered test tube and extracted with 5 x 10 ml quantities of phosphate buffer pH 6.8. The extracts were filtered and collected into 100 ml of volumetric flask and made up to volume with phosphate buffer pH 6.8. And the solution were subsequently diluted suitably with phosphate buffer pH 6.8 and assayed for Etodolac IR tablets at 274 nm and the results are given in tablet. At least 9 must assay within ±15% of the declared potency and none may exceed ±25%. The results are given in table no. 34.

ASSAY PREPARATION

Weigh and finely powder not less than 20 Etodolac IR tablets from each formulation. Remaining procedure is same as like content uniformity. Limit is Etodolac tablets contain not less than 90.0 percent and more than 110.0 percent of the labeled amount of Etodolac.

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TABLET DISINTEGRATION TEST

The disintegration time of Etodolac IR tablets was determined in distilled water using Remi Tablet Disintegration test machine of USP/IP standard. The results are given in table no. 34. If one or two tablets fail to disintegrate, the test is repeated using 12 tablets. For most uncoated tablets, the IP requires that the tablets disintegrate in 15 minutes.

DISSOLUTION TEST

The dissolution rate of Etodolac IR tablets from various tablets prepared were studied using USP XXI Dissolution Rate Test Apparatus. (Lab India Disso 2000) employing paddle stirrer, as per dissolution rate prescribed in IP, for the above tablets the phosphate buffer of pH 6.8 (900 ml) were used as dissolution fluids for Etodolac IR tablets. In each test one tablet, a speed 100 rpm rotations and a temperature of 37°C ± 1°C were employed. A 10 ml aliquot of dissolution medium was withdrawn at different time interval suitable diluted and assayed spectrophotometrically at 274 nm for Etodolac. The percentage of drug dissolved at various time intervals 5, 10, 15, 20, 30, 45 min was calculated and plotted against time. The results are given in table no. 35 to 41.

TABLE NO. 33: APPEARANCE, THICKNESS AND DIAMETER OF ALL FORMULATED ETODOLAC IR TABLETS (F1- F10)

S. No.	Formulation code	Appearance	Diameter (mm)	Thickness (mm)
1.	F1	*Appearance: Etodolac IR tablets were off-white, flat circular and uncoated with Mark SRIPMS on one surface of the tablet.	12.5 ± 0.05	4.83 ± 0.75
2.	F2		12.6 ± 0.11	4.83 ± 0.75
3.	F3		12.4 ± 0.1	4.64 ± 0.75
4.	F4		12.5 ± 0.05	4.47 ± 0.75
5.	F5		12.5 ± 0.05	4.48 ± 0.09
6.	F6		12.4 ± 0.05	4.16 ± 0.18
7.	F7		12.8 ± 0.26	4.18 ± 0.07
8.	F8		12.5 ± 0.10	4.33 ± 0.06
9.	F9		12.6 ± 0.01	4.57 ± 0.04
10.	F10		12.6 ± 0.01	4.39 ± 0.06

TABLE NO. 34: HARDNESS, FRIABILITY, DISINTEGRATION TIME AND WEIGHT VARIATION AND CONTENT UNIFORMITY OF ALL FORMULATED ETODOLAC IR TABLETS (F1-F10) AND MARKET SAMPLE (MS)

S. No.	Formulation code	Hardness (Kg/Cm^2)	Friability (%)	Disintegration Time (Min and Sec)	Average Weight (Limit range: 465.5 - 514.5)	Content uniformity (%)
1.	F1	5.3 ± 0.10	0.78	38.5 ± 1.29	491.6	93.2
2.	F2	5.0 ± 0.20	0.62	14.75 ± 0.44	485.1	97.1
3.	F3	4.8 ± 0.10	0.81	13.00 ± 0.67	493.2	96.4
4.	F4	5.2 ± 0.1	0.57	11.51 ± 0.22	497.0	95.5
5.	F5	4.9 ± 0.15	0.72	10.94 ± 0.08	489.5	94.3
6.	F6	4.3 ± 0.10	0.58	10.16 ± 0.09	493.4	96.8
7.	F7	5.5 ± 0.10	0.73	9.60 ± 0.06	488.7	101.1
8.	F8	5.1 ± 0.15	0.69	8.63 ± 0.15	492.3	98.6
9.	F9	5.6 ± 0.10	0.85	4.70 ± 0.05	491.4	98.9
10.	F10	4.8 ± 0.15	0.83	4.50 ± 0.15	490.9	99.5
11.	MS	4.9 ± 0.10	0.81	7.51 ± 0.11	-	-

TABLE NO. 35: DISSOLUTION PROFILE OF ETODOLAC IR TABLETS CONTAINING 2%, 4%, 6% OF CROSPOVIDONE AND SODIUM STARCH GLYCOLATE BY INTRAGRANULAR (F2, F3, AND F4) AND CONTROL TABLET (F1)

S. no.	Time in mins	% of Etodolac Drug Release in pH 6.8			
		F1	F2	F3	F4
1.	5	12.3 ± 1.68	17.5 ± 1.16	19.1 ± 1.35	21.2 ± 1.40
2.	10	13.1 ± 1.15	28.1 ± 0.85	30.2 ± 1.32	31.4 ± 1.15
3.	15	14.7 ± 1.08	38.7 ± 1.46	40.7 ± 0.97	41.6 ± 0.99
4.	30	16.8 ± 0.96	63.5 ± 1.58	68.6 ± 1.07	70.8 ± 1.68
5	45	18.6 ± 1.04	74.8 ± 1.45	77.5 ± 1.03	80.1 ± 1.43

FIGURE NO. 8: *IN VITRO* DRUG RELEASE PROFILE OF ETODOLAC IR TABLETS, CONTAINING 2%, 4%, 6% OF CROSPOVIDONE AND SODIUM STARCH GLYCOLATE BY INTRAGRANULAR (F2, F3, AND F4) AND CONTROL TABLET (F1)

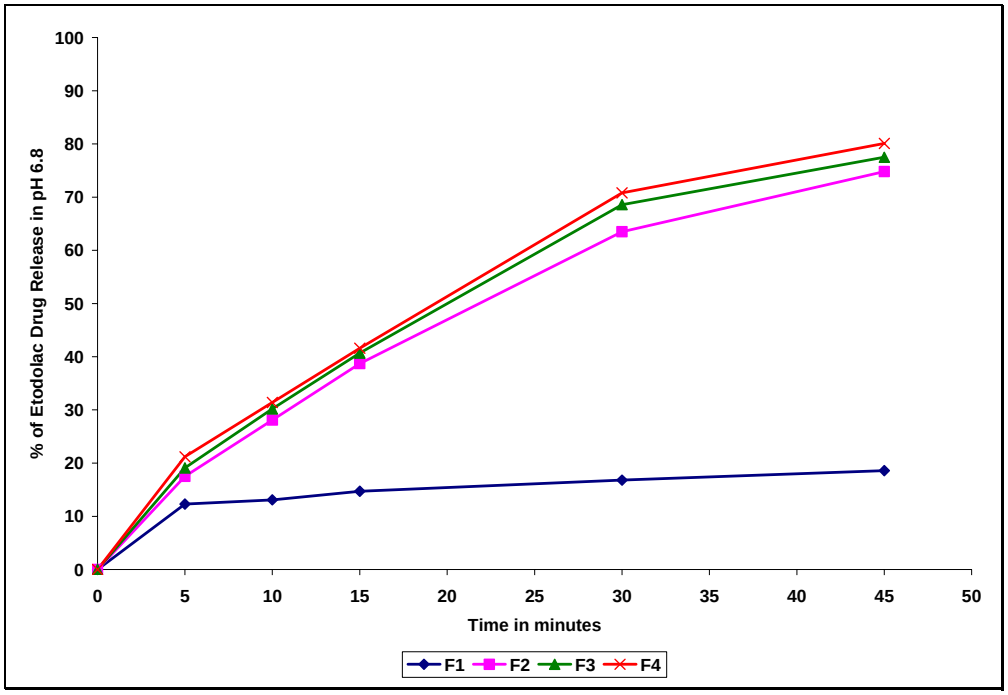


TABLE NO. 36: DISSOLUTION PROFILE OF ETODOLAC IR TABLETS CONTAINING 2%, 4%, 6% OF CROSPOVIDONE AND SODIUM STARCH GLYCOLATE BY EXTRAGRANULAR (F5, F6, AND F7)

S. No.	Time in Mins	% of Etodolac Drug Release in pH 6.8		
		F5	F6	F7
1.	5	24.5 ± 1.71	28.6 ± 1.18	29.4 ± 1.06
2.	10	48.5 ± 1.08	54.6 ± 1.18	55.9 ± 1.62
3.	15	56.1 ± 0.68	59.8 ± 1.03	60.9 ± 0.97
4.	30	65.4 ± 0.85	70.1 ± 0.74	71.8 ± 1.02
5.	45	70.0 ± 0.67	75.91 ± 0.65	77.95 ± 1.12

FIGURE NO. 9: *IN VITRO* DRUG RELEASE PROFILE OF ETODOLAC IR TABLETS, CONTAINING 2%, 4%, 6% OF CROSPOVIDONE AND SODIUM STARCH GLYCOLATE BY EXTRAGRANULAR (F5, F6, AND F7)

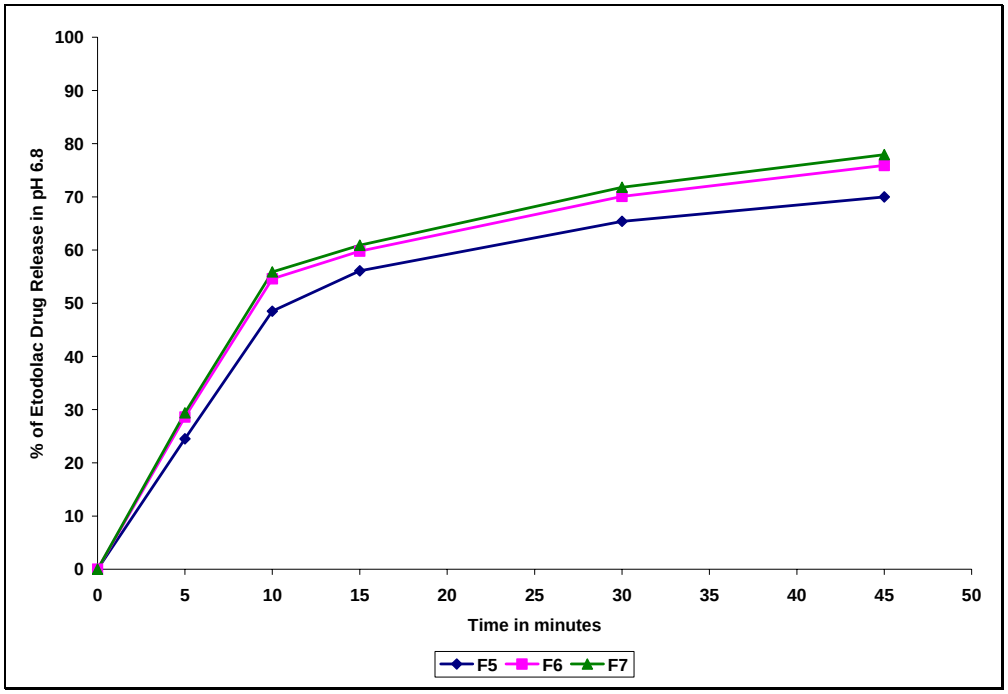


TABLE NO. 37: DISSOLUTION PROFILE OF ETODOLAC IR TABLETS CONTAINING 2%, 4%, 6% OF CROSPOVIDONE AND SODIUM STARCH GLYCOLATE BY INTRA AND EXTRAGRANULAR (F8, F9, AND F10)

S. No.	Time in Mins	% of Etodolac Drug Release in pH 6.8		
		F8	F9	F10
1.	5	46.3 ± 1.41	62.4 ± 1.72	78.9 ± 1.85
2.	10	61.5 ± 1.75	76.1 ± 1.84	85.0 ± 2.83
3.	15	79.6 ± 0.98	88.5 ± 2.56	92.9 ± 1.72
4.	30	87.6 ± 1.08	93.0 ± 1.68	97.7 ± 1.57
5.	45	92.6 ± 1.52	96.1 ± 1.54	100.8 ± 1.89

FIGURE NO. 10: *IN VITRO* DRUG RELEASE PROFILE OF ETODOLAC IR TABLETS CONTAINING 2%, 4%, 6% OF CROSPOVIDONE AND SODIUM STARCH GLYCOLATE BY INTRA AND EXTRAGRANULAR (F8, F9, AND F10)

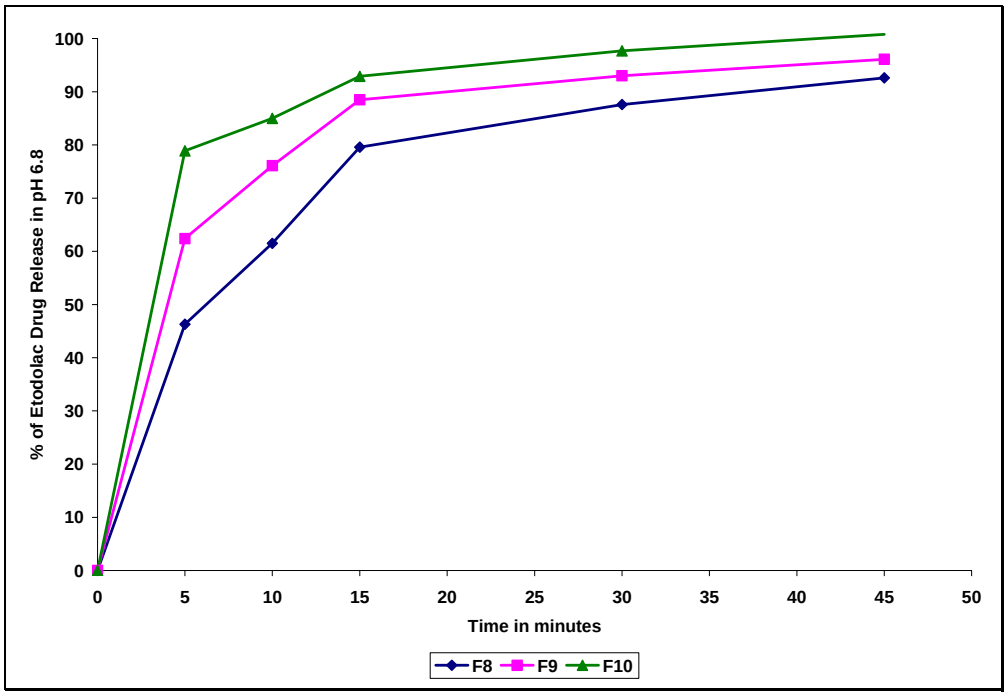


TABLE NO. 38: DISSOLUTION PROFILE OF ALL FORMULATED ETODOLAC IR TABLETS AND MARKET SAMPLE

S. No	Time in mins	% of drug release										
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	MI
1.	5	12.3 ± 1.68	17.5 ± 1.16	19.1 ± 1.35	21.2 ± 1.40	24.5 ± 1.71	28.6 ± 1.18	29.4 ± 1.06	46.3 ± 1.41	62.4 ± 1.72	78.9 ± 1.85	21.6
2.	10	13.1 ± 1.15	28.1 ± 0.85	30.2 ± 1.32	31.4 ± 1.15	48.5 ± 1.08	54.6 ± 1.18	55.9 ± 1.62	61.5 ± 1.75	76.1 ± 1.84	85.0 ± 2.83	46.3
3.	15	14.7 ± 1.08	38.7 ± 1.46	40.7 ± 0.97	41.6 ± 0.99	56.1 ± 0.68	59.8 ± 1.03	60.9 ± 0.97	79.6 ± 0.98	88.5 ± 2.56	92.9 ± 1.72	54.9
4.	30	16.8 ± 0.96	63.5 ± 1.58	68.6 ± 1.07	70.8 ± 1.68	65.4 ± 0.85	70.1 ± 0.74	71.8 ± 1.02	87.6 ± 1.08	93.0 ± 1.68	97.7 ± 1.57	67.5
5.	45	18.6 ± 1.04	74.8 ± 1.45	77.5 ± 1.03	80.1 ± 1.43	70.0 ± 0.67	75.91 ± 0.65	77.95 ± 1.12	92.6 ± 1.52	96.1 ± 1.54	100.8 ± 1.89	84.7

FIGURE NO. 11: *IN VITRO* DRUG RELEASE PROFILE OF ALL FORMULATED ETODOLAC IR TABLETS AND MARKET SAMPLE

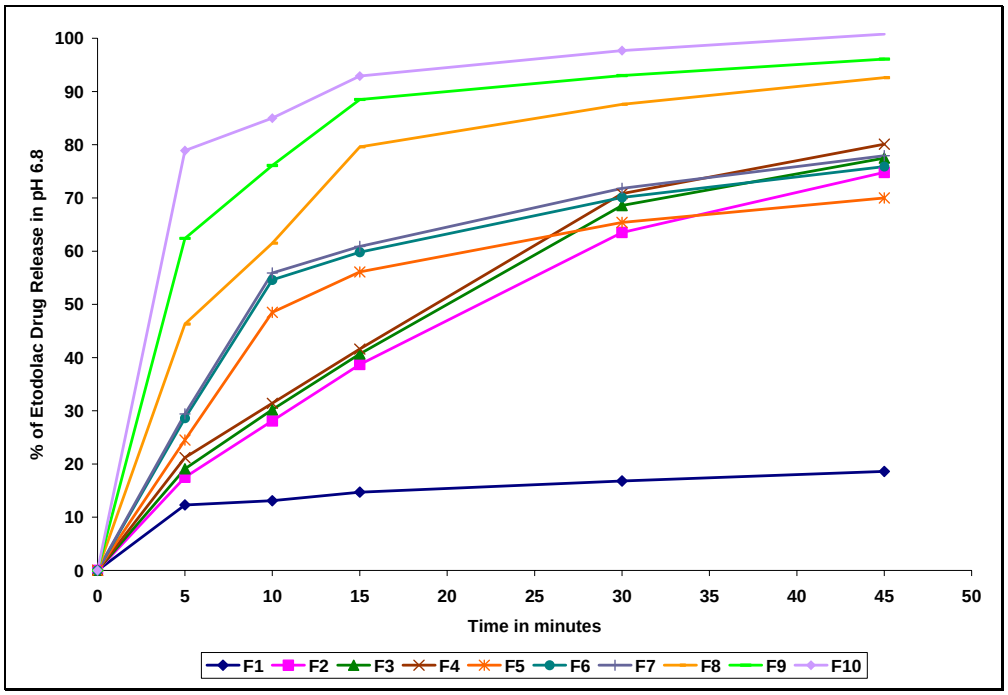


TABLE NO. 39: DISSOLUTION PROFILE COMPARISON OF ETODOLAC IR TABLETS CONTAINING 2%, 4%, 6% OF CROSPOVIDONE AND SODIUM STARCH GLYCOLATE BY "INTRAGRANULAR" (F2, F3, AND F4) AND "EXTRAGRANULAR" (F5, F6, AND F7) AND CONTROL TABLET (F1)

S. No.	Time in Mins	% of Etodolac drug release in pH 6.8						
		F1	F2	F3	F4	F5	F6	F7
1.	5	12.3 ± 1.68	17.5 ±1.16	19.1 ± 1.35	21.2 ± 1.40	24.5 ±1.71	28.6 ± 1.18	29.4 ± 1.06
2.	10	13.1 ± 1.15	28.1 ± 0.85	30.2 ± 1.32	31.4 ± 1.15	48.5 ± 1.08	54.6 ± 1.18	55.9 ± 1.62
3.	15	14.7 ± 1.08	38.7 ± 1.46	40.7 ± 0.97	41.6 ± 0.99	56.1 ± 0.68	59.8 ± 1.03	60.9 ± 0.97
4.	30	16.8 ± 0.96	63.5 ± 1.58	68.6 ± 1.07	70.8 ± 1.68	65.4 ± 0.85	70.1 ± 0.74	71.8 ± 1.02
5.	45	18.6 ± 1.04	74.8 ± 1.45	77.5 ± 1.03	80.1 ± 1.43	70.0 ± 0.67	75.91 ± 0.65	77.95 ± 1.12

FIGURE NO 12: *IN VITRO* DRUG RELEASE PROFILE COMPARISON OF ETODOLAC IR TABLETS CONTAINING 2%, 4%, 6% OF CROSPOVIDONE AND SODIUM STARCH GLYCOLATE BY

"INTRAGRANULAR" (F2, F3, AND F4) AND "EXTRAGRANULAR" (F5, F6, AND F7) AND CONTROL TABLET (F1)

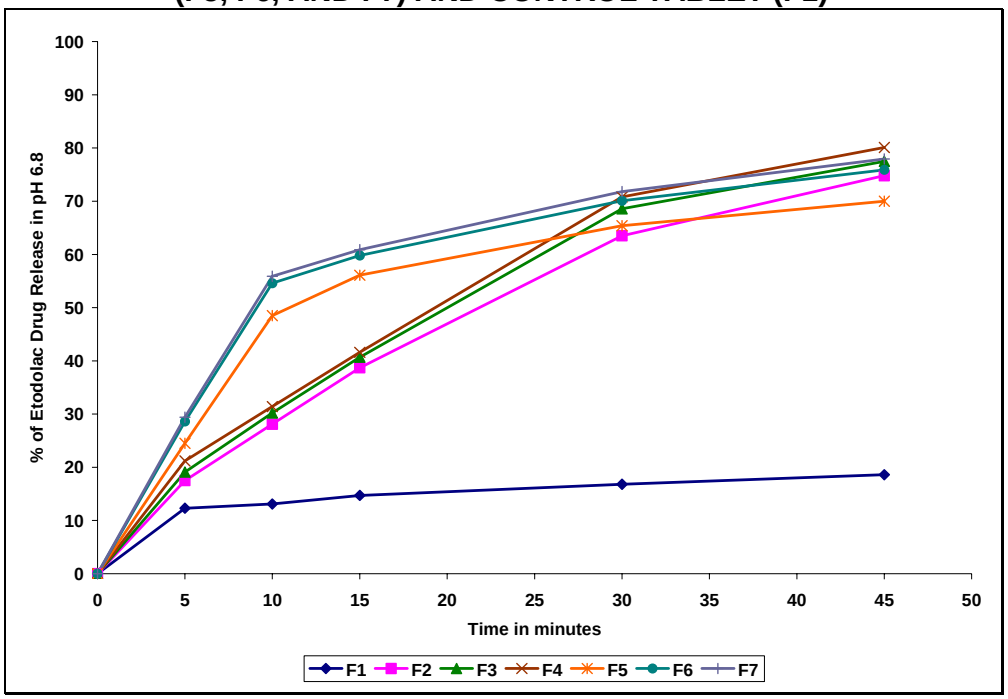


TABLE NO. 40: DISSOLUTION PROFILE COMPARISON OF ETODOLAC IR TABLETS CONTAINING 2%, 4%, 6% OF CROSPOVIDONE AND SODIUM STARCH GLYCOLATE BY "INTRAGRANULAR" (F2, F3, AND F4) AND "INTRA + EXTRAGRANULAR" (F8, F9 AND F10) AND CONTROL TABLET (F1)

S. No.	Time in Mins	% of Etodolac drug release in pH 6.8						
		F1	F2	F3	F4	F8	F9	F10
1.	5	12.3 ± 1.68	17.5 ± 1.16	19.1 ± 1.35	21.2 ± 1.40	46.3 ± 1.41	62.4 ± 1.72	78.9 ± 1.85
2.	10	13.1 ± 1.15	28.1 ± 0.85	30.2 ± 1.32	31.4 ± 1.15	61.5 ± 1.75	76.1 ± 1.84	85.0 ± 2.83
3.	15	14.7 ± 1.08	38.7 ± 1.46	40.7 ± 0.97	41.6 ± 0.99	79.6 ± 0.98	88.5 ± 2.56	92.9 ± 1.72
4.	30	16.8 ± 0.96	63.5 ± 1.58	68.6 ± 1.07	70.8 ± 1.68	87.6 ± 1.08	93.0 ± 1.68	97.7 ± 1.57
5.	45	18.6 ± 1.04	74.8 ± 1.45	77.5 ± 1.03	80.1 ± 1.43	92.6 ± 1.52	96.1 ± 1.54	100.8 ± 1.89

FIGURE NO. 13: *IN VITRO* DRUG RELEASE PROFILE COMPARISON OF ETODOLAC IR TABLETS CONTAINING 2%, 4%, 6% OF CROSPOVIDONE AND SODIUM STARCH GLYCOLATE BY "INTRAGRANULAR" (F2, F3, AND F4) AND "INTRA + EXTRAGRANULAR" (F8, F9, AND F10) AND CONTROL TABLET

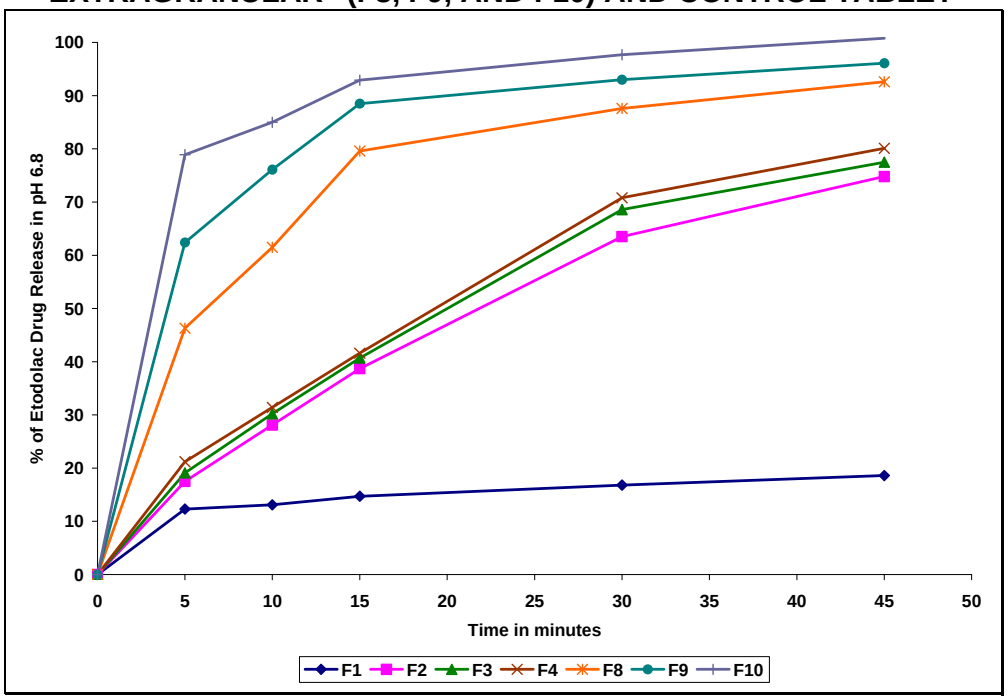


TABLE NO. 41: DISSOLUTION PROFILE COMPARISON OF ETODOLAC IR TABLETS CONTAINING 2%, 4%, 6% OF CROSPOVIDONE AND SODIUM STARCH GLYCOLATE BY "EXTRAGRANULAR" (F5, F6, AND F7) AND "INTRA + EXTRAGRANULAR" (F8, F9, AND F10) AND CONTROL TABLET (F1)

S. No.	Time in Mins	% of Etodolac drug release in pH 6.8						
		F1	F5	F6	F7	F8	F9	F10
1.	5	12.3 ± 1.68	24.5 ± 1.71	28.6 ± 1.18	29.4 ± 1.06	46.3 ± 1.41	62.4 ± 1.72	78.9 ± 1.85
2.	10	13.1 ± 1.15	48.5 ± 1.08	54.6 ± 1.18	55.9 ± 1.62	61.5 ± 1.75	76.1 ± 1.84	85.0 ± 2.83
3.	15	14.7 ± 1.08	56.1 ± 0.68	59.8 ± 1.03	60.9 ± 0.97	79.6 ± 0.98	88.5 ± 2.56	92.9 ± 1.72
4.	30	16.8 ± 0.96	65.4 ± 0.85	70.1 ± 0.74	71.8 ± 1.02	87.6 ± 1.08	93.0 ± 1.68	97.7 ± 1.57
5.	45	18.6 ± 1.04	70.0 ± 0.67	75.91 ± 0.65	77.95 ± 1.12	92.6 ± 1.52	96.1 ± 1.54	100.8 ± 1.89

FIGURE NO. 14: *IN VITRO* DRUG RELEASE PROFILE COMPARISON OF ETODOLAC IR TABLETS CONTAINING 2%, 4%, 6% OF CROSPOVIDONE AND SODIUM STARCH GLYCOLATE BY "EXTRAGRANULAR" (F5, F6, AND F7) AND "INTRA + EXTRAGRANULAR" (F8, F9, AND F10) AND CONTROL TABLET (F1)

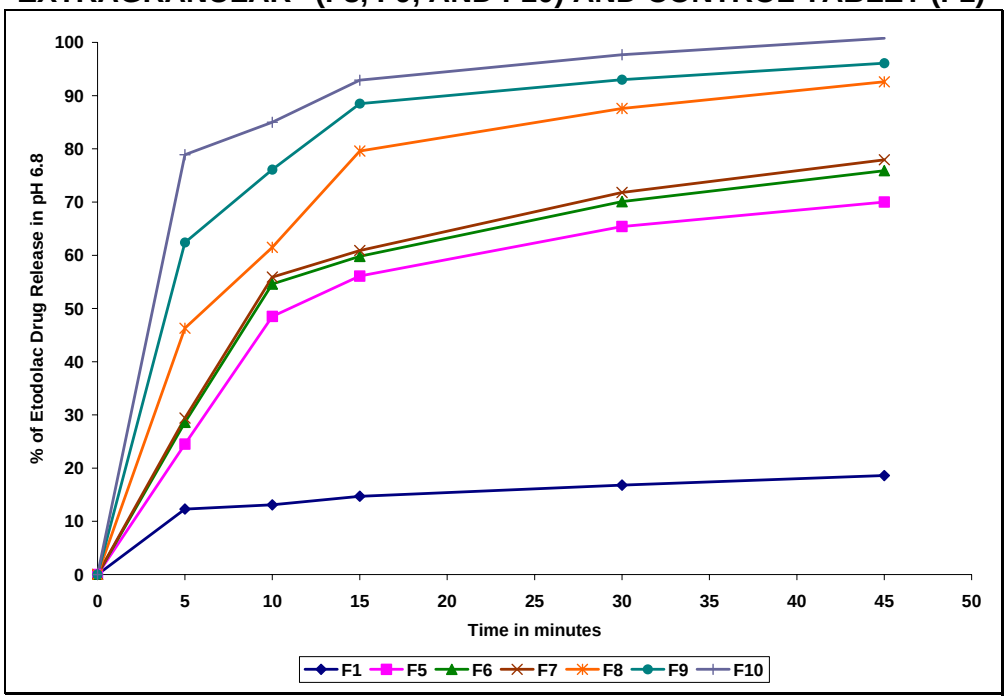


TABLE NO. 42: t_{50} AND t_{90} OF ALL FORMULATED ETODOLAC IR TABLETS (F1-F10)

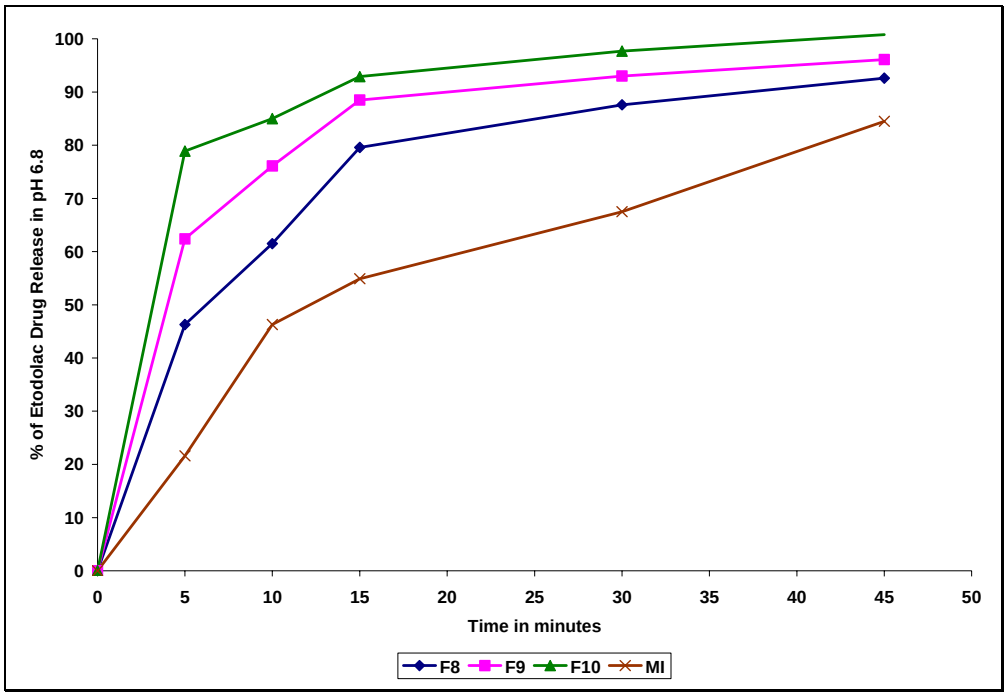
S. No.	Formulation Code	t_{50}	t_{90}
		pH 6.8	
1.	F1	-	-
2.	F2	22.75	-
3.	F3	20.00	-
4.	F4	19.00	-
5.	F5	11.25	-
6.	F6	9.00	-

7.	F7	8.00	
8.	F8	6.25	30
9.	F9	4.00	17.5
10.	F10	2.30	8.5

TABLE NO. 43: DISSOLUTION PROFILE COMPARISON OF ETODOLAC IR TABLETS CONTAINING 2%, 4%, 6% OF CROSPOVIDONE AND SODIUM STARCH GLYCOLATE BY "INTRA + EXTRAGRANULAR" (F8, F9, AND F10) AND MARKET SAMPLE (MS)

S. No.	Time in Mins	% of Etodolac drug release in pH 6.8			
		F8	F9	F10	MS
1.	5	46.3 ± 1.41	62.4 ± 1.72	78.9 ± 1.85	21.6
2.	10	61.5 ± 1.75	76.1 ± 1.84	85.0 ± 2.83	46.3
3.	15	79.6 ± 0.98	88.5 ± 2.56	92.9 ± 1.72	54.9
4.	30	87.6 ± 1.08	93.0 ± 1.68	97.7 ± 1.57	67.5
5.	45	92.6 ± 1.52	96.1 ± 1.54	100.8 ± 1.89	84.5

FIGURE NO. 15: *IN VITRO* DRUG RELEASE PROFILE COMPARISON OF ETODOLAC IR TABLETS CONTAINING 2%, 4%, 6% OF CROSPOVIDONE AND SODIUM STARCH GLYCOLATE BY "INTRA + EXTRAGRANULAR" (F8, F9, AND F10) AND MARKET SAMPLE (MS)



Chapter 10 Evaluation of Etodolac IR Tablets

STABILITY STUDIES

REAL TIME STABILITY STUDY

Among all formulated Etodolac immediate release tablets, formulation F10 was selected based on its release in the dissolution medium phosphate buffer pH 6.8 and it is kept in the real time stability chamber for stability studies. After specified period of time, the samples were collected and the percentage of drug release and assay was calculated and the percentage of drug release and assay was calculated and the graph was plotted between time vs. percentage of Etodolac released. The results were given in the table no. 44 to 48 and figure no. 16.

Accelerated stability study

Among all formulated Etodolac immediate release tablets, formulation F10 was selected based on its release in the dissolution medium, and phosphate buffer pH 6.8 and it is kept in the accelerated stability chamber for stability studies. After specified period of time, the samples were collected and the percentage of drug release and assay was calculated and the graph was plotted between time vs. percentage of Etodolac released. The results were given in the table no. 44 to 48 and figure no. 17.

TABLE NO. 44: STABILITY STUDY TEST TO BE CONDUCTED FOR ETODOLAC IR TABLET DOSAGE FORM

S. No.	Test	Stability criteria
1.	Assay	90.0 – 110.0 % of label
2.	Degradation production	Not more than 0.3% each
3.	Dissolution	Q = 80% in 45 min (USP acceptance criteria)
4.	Appearance	No significant difference from a control stored at $5^{o}C$
5.	Disintegration	Based on dissolution
6.	Hardness	-
7.	Content uniformity	Within the limit
8.	Friability	Based on hardness
9.	Water content (Karl Fischer titration)	-

TABLE NO. 45: COMPARISON OF PHYSICAL PARAMETER OF STABILITY FORMULATION (F10) IN REAL TIME AND ACCELERATED STABILITY STUDY WITH INITIAL MONTH

Parameter	Initial / zero month	Long term/real time stability study			Accelerated stability study		
		1st month	2nd month	3rd month	1st month	2nd month	3rd month
Appearance	*	*	*	*	*	*	*
Thickness (mm)	4.39 ± 0.06	4.39 ± 0.06	4.39 ± 0.06	4.39 ± 0.065	4.39 ± 0.06	4.39 ± 0.06	4.39 ± 0.065
Diameter (mm)	12.6 ± 0.01	12.6 ± 0.0108	12.6 ± 0.0108	12.6 ± 0.0108	12.6 ± 0.0108	12.6 ± 0.0108	12.6 ± 0.0108
Hardness (kg/cm^2)	4.8 ± 0.15	4.8 ± 0.15	4.8 ± 0.15	4.8 ± 0.15	4.8 ± 0.15	4.8 ± 0.15	4.8 ± 0.15
Friability (% w/w)	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Disintegration time (min/sec)	4.50 ± 0.15	4.61 ± 0.1	4.62 ± 0.1	4.62 ± 0.15	4.61 ± 0.15	4.71 ± 0.15	4.71 ± 0.15

* white, flat, circular, beveledged, uncoated tablet with a mark SRIPMS on one surface.

TABLE NO. 46: DISSOLUTION PROFILE OF STABILITY FORMULATION (F10) IN REAL TIME STABILITY CONDITION

Time in mins	% of drug released			
	Initial / zero month	1st month	2nd month	3rd month
5	78.9 ± 1.85	75.9 ± 2.15	74.1 ± 2.35	73.9 ± 2.94
10	85.0 ± 2.83	84.1 ± 2.35	82.5 ± 2.56	81.2 ± 2.69
15	92.9 ± 1.72	91.9 ± 1.62	91.5 ± 1.58	90.9 ± 1.84
30	97.7 ± 1.57	95.4 ± 1.64	94.6 ± 1.68	92.9 ± 1.62
45	100.8 ± 1.89	99.8 ± 1.59	99.6 ± 1.25	99.4 ± 1.05

FIGURE NO. 16: *IN VITRO* DRUG RELEASE PROFILE OF STABILITY FORMULATION (F10) IN REAL TIME STABILITY CONDITION

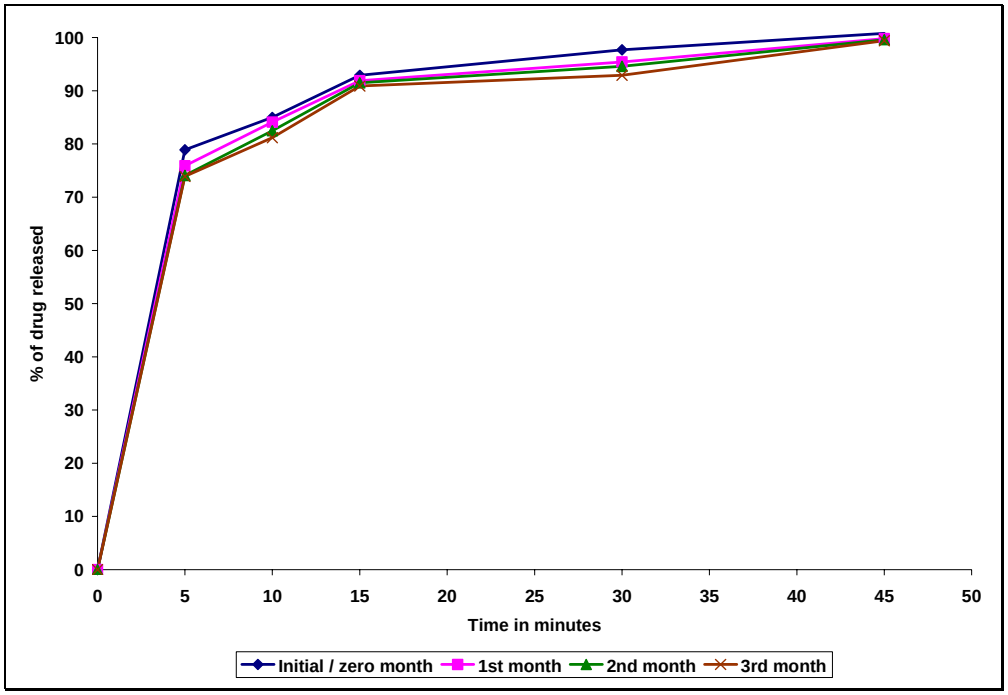


TABLE NO. 47: DISSOLUTION PROFILE OF STABILITY FORMULATION (F10) IN ACCELERATED STABILITY CONDITION

Time in mins	% of drug released			
	Initial / zero month	1st month	2nd month	3rd month
5	78.9 ± 1.85	75.9 ± 4.50	74.1 ± 3.25	73.9 ± 1.94
10	85.0 ± 2.83	83.1 ± 4.15	82.5 ± 2.46	80.2 ± 2.98
15	92.9 ± 1.72	91.4 ± 1.95	90.1 ± 1.56	89.9 ± 1.96
30	97.7 ± 1.57	94.6 ± 1.60	93.2 ± 1.40	91.5 ± 1.92
45	100.8 ± 1.89	98.2 ± 0.98	98.4 ± 1.24	97.4 ± 1.21

FIGURE NO. 17: *IN VITRO* DRUG RELEASE PROFILE OF STABILITY FORMULATION (F10) IN ACCELERATED STABILITY CONDITION

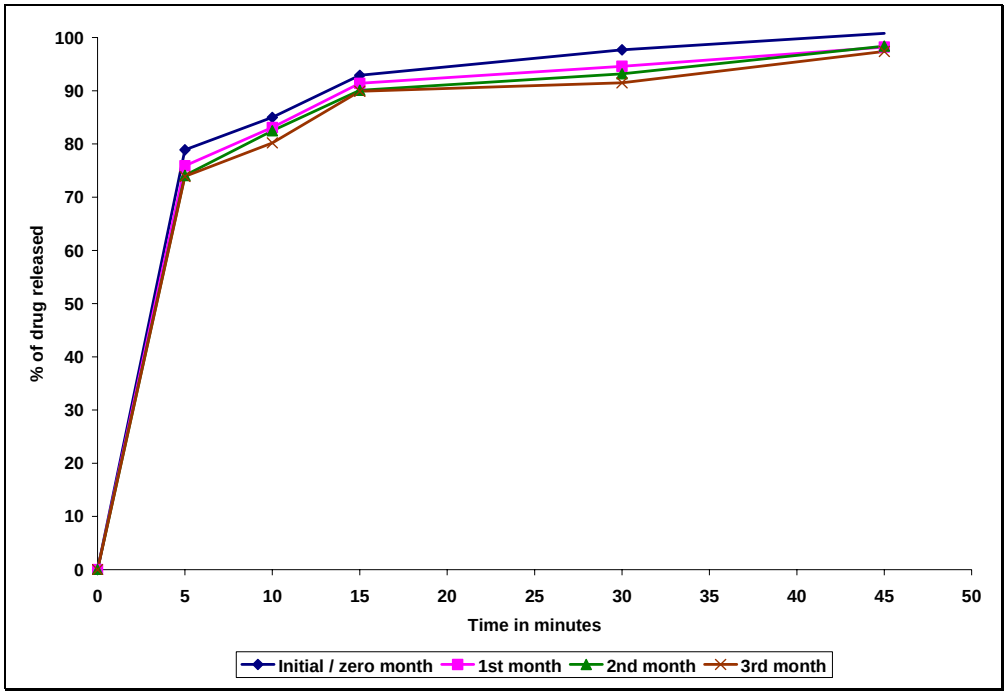


TABLE NO. 48: ASSAY OF STABILITY FORMULATION (F10) IN REAL TIME AND ACCELERATED STABILITY CONDITION

Stability Condition	Initial / zero month		Amount of drug / tablet					
			1st month		2nd month		3rd month	
	Mg	%	Mg	%	Mg	%	Mg	%
Real time	300.78	101.8	300.14	100.12	299.91	100.01	299.78	99.87
Accelerate	300.78	101.8	300.25	100.05	299.75	99.92	299.04	99.68

COMPATIBILITY STUDIES

Preservation of the chemical integrity of the drug substance during intended shelf life of the product is the fundamental prerequisite toward successful formulation of any drug delivery system. The crucial requirement is thus the confirmation of the absence of chemical interaction between the drug and the excipients. Many techniques like diffuse reflectance spectroscopy, accelerated storage tests TLC, IR and thermal methods are employed for the detection of potential interaction.

THIN LAYER CHROMATOGRAM

A thin layer chromatographic method was also carried to study the interaction between the drug and excipient and also to confirm the chemical stability of the Etodolac drug in IR tablet. For this, the pure Etodolac drug and the formulated Etodolac IR tablet with various excipients by Wet granulation method were subjected to chromatographic studies.

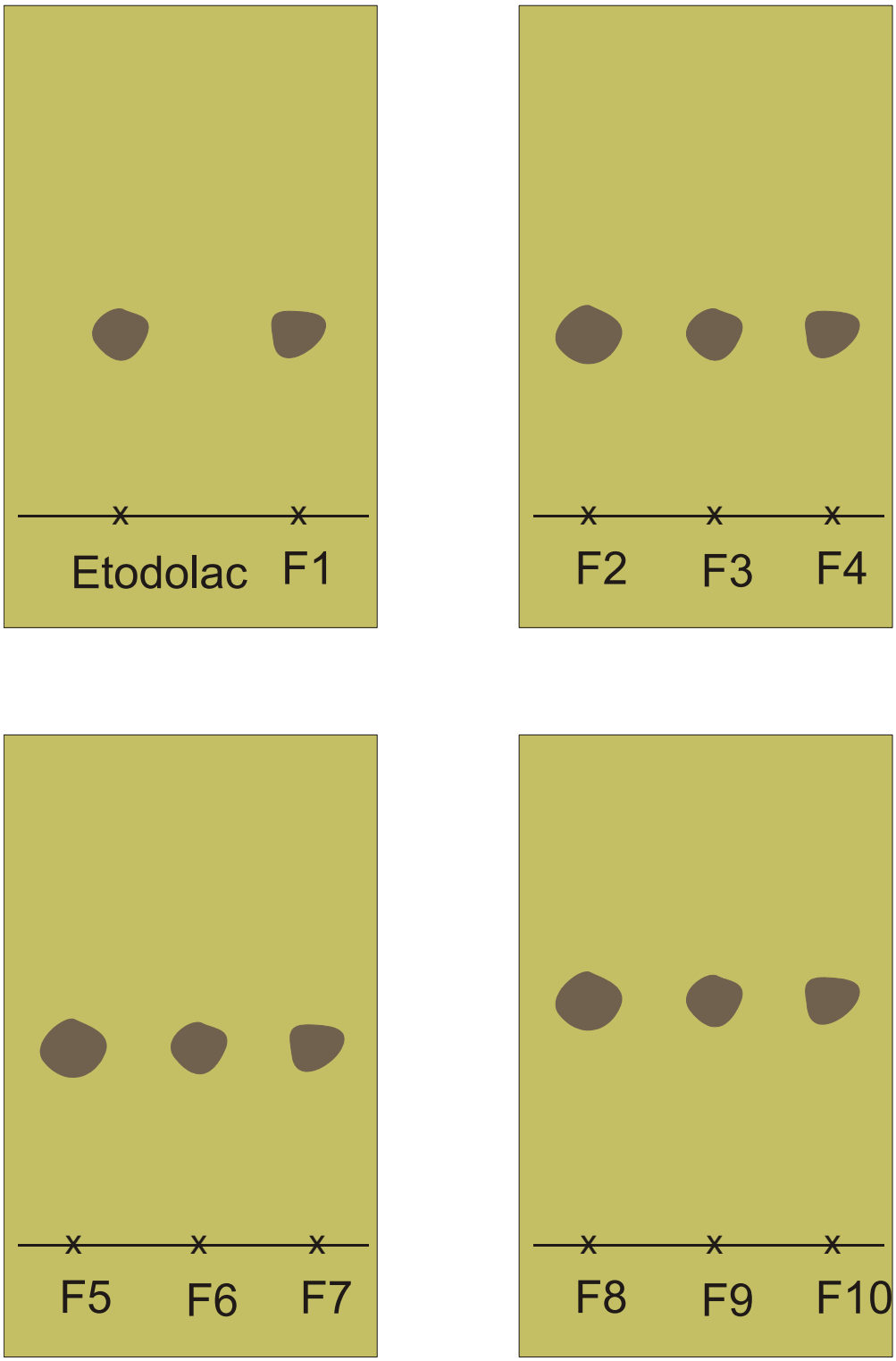
The following TLC system was used

Precoated TLC plates	:	Manufactured by SD Fine Chemicals Ltd., Mumbai.
Adsorbant layer	:	Silica gel GF_{254}
Layer thickness	:	0.22 mm
Size	:	10 × 20 cm
Separation technique	:	Ascending
Chamber saturation rate	:	The chamber was lined on 3 sides with filter paper saturated for 30 minutes
Solvent front	:	5.3 cm
Solvent system	:	Glacial acetic acid:Ethanol:Toulene (0.5:30:70)
Preparation of samples	:	Dissolve 10 mg of the Etodolac in acetone and dilute to 10 ml with the same solvent. The resultant solution is used for spotting.
Amount Applied	:	10µl.
Detection	:	Short and long wave length of UV light.

The Rf values obtained are given in the table no. 49.

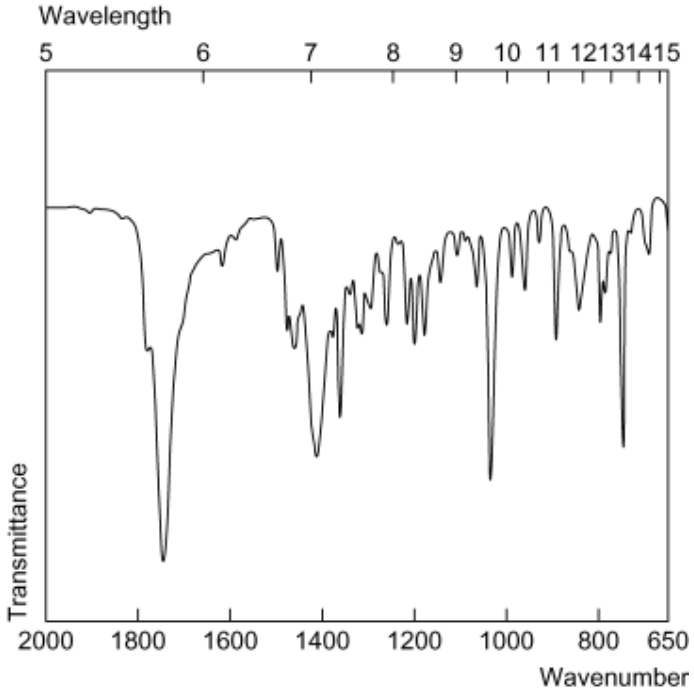
TABLE NO. 49: TLC DATA FOR ETODOLAC PURE DRUG AND ETODOLAC IR TABLETS WITH OTHER EXCIPIENTS

SAMPLE	Rf VALUES	NUMBER OF SPOTS
Etodolac (pure)	0.49	Single
Etodolac IR tablet with excipients		
F1 (control)	0.49	Single
F2 (with SD)	0.51	Single
F3 (with SD)	0.51	Single
F4 (with SD)	0.51	Single
F5 (with SD)	0.54	Single
F6 (with SD)	0.54	Single
F7 (with SD)	0.54	Single
F8 (with SD)	0.52	Single
F9 (with SD)	0.52	Single
F10 (with SD)	0.52	Single


Etodolac
F1
F2
F3
F4
F5
F6
F7
F8
F9
F10

INFRARED SPECTRUM

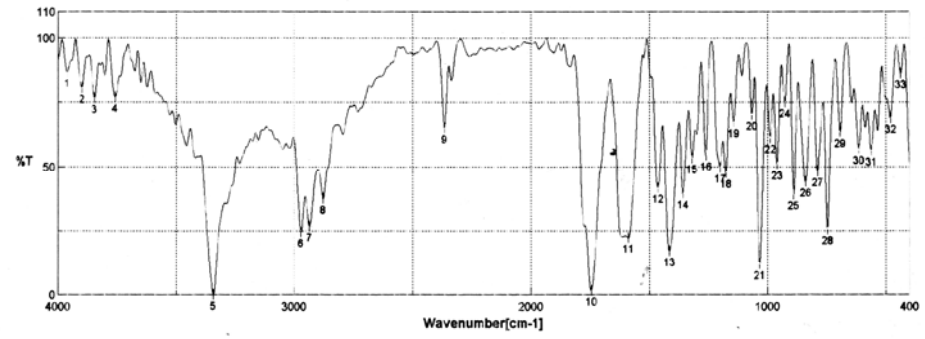
Principal peaks at wavenumbers 1746, 1412, 1034, 748 cm^{-1} (KBr pellet).



IR SPECTRAL ANALYSIS

Fourier Transform infrared (FT-IR) spectra of the samples were obtained in the range of 700-1800 cm^{-1} using a FT- IR Jasco 410 spectrophotometer (Jasco. Essex) by the KBr disc method. The IR spectra of various immediate release Etodolac tablets and pure drug of Etodolac were obtained in figure no. 18 to 21.

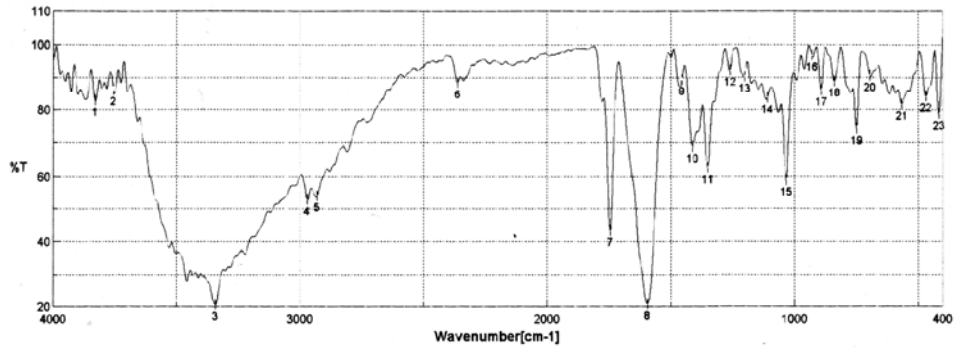
FIGURE NO. 18: IR SPECTRA OF ETODOLAC PURE DRUG



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	9/29/2008 0:16PM	Update	9/30/2008 10:22AM
Operator	C.Geetha		
File Name	Pure drug -etodolac		
Sample Name	Pure drug -etodolac		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3981.07	86.7111	2	3899.36	80.5063	3	3844.4	76.7063	4	3756.65	77.0734	5	3343	0.220293
6	2970.8	24.513	7	2936.09	26.7931	8	2878.24	37.6298	9	2365.26	65.1328	10	1745.26	1.8692
11	1589.06	22.3477	12	1463.71	41.809	13	1415.49	17.0945	14	1357.64	39.5841	15	1319.07	53.4311
16	1261.22	54.447	17	1201.43	49.8968	18	1176.36	47.7712	19	1142.62	67.3192	20	1065.48	70.1675
21	1031.73	12.0879	22	988.339	61.1587	23	959.412	50.993	24	926.628	74.9799	25	889.987	39.3372
26	840.812	44.2617	27	789.707	48.3899	28	747.281	25.5531	29	693.284	83.521	30	614.217	56.8439
31	562.148	56.3566	32	480.188	68.8925	33	437.762	86.2866						

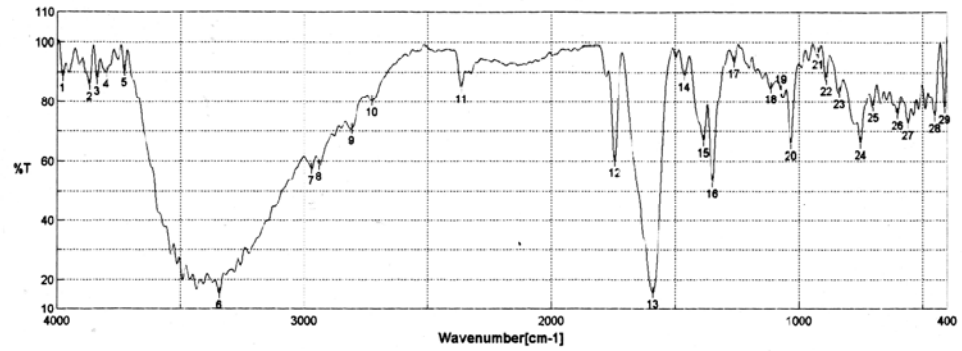
FIGURE NO. 19: IR SPECTRA OF FORMULATION F8 (DRUG + EXCIPIENT)



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	10/24/2008 3:20PM	Update	10/30/2008 11:55AM
Operator	C.Geetha		
File Name	F8		
Sample Name	F8		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3828.97	82.8221	2	3755.69	86.1573	3	3343	20.8018	4	2971.77	52.7395	5	2932.23	53.8785
6	2382.37	86.3992	7	1745.26	43.2679	8	1594.84	21.0523	9	1455.03	89.3966	10	1412.6	68.9633
11	1351.86	62.5785	12	1259.29	92.2312	13	1201.43	90.1249	14	1107.9	83.6356	15	1032.69	58.7039
16	929.521	96.8786	17	891.916	86.0671	18	837.919	86.9061	19	746.245	74.1622	20	693.284	90.6147
21	568.005	81.7734	22	468.617	84.2106	23	415.585	78.6618						

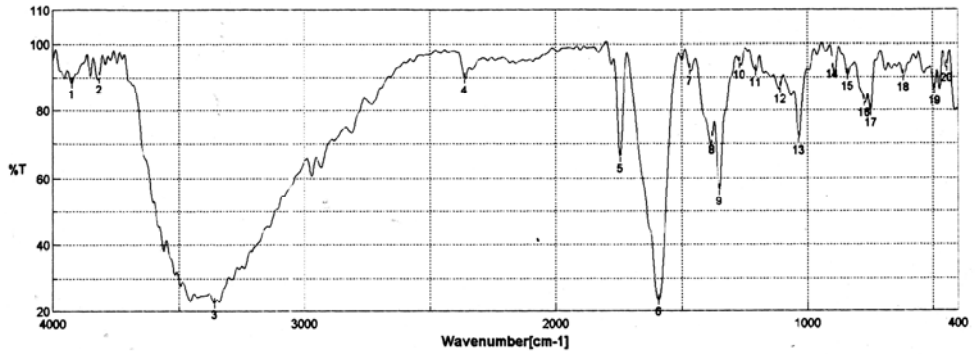
FIGURE NO. 20: IR SPECTRA OF FORMULATION F9 (DRUG + EXCIPIENT)



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	10/24/2008 3:22PM	Update	10/30/2008 11:58AM
Operator	C.Geetha		
File Name	F9		
Sample Name	F9		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3977.46	88.7225	2	3870.43	85.8539	3	3838.61	87.7165	4	3800.04	90.0777	5	3728.69	90.5822
6	3343	15.4106	7	2971.77	57.4298	8	2940.91	58.8566	9	2807.85	70.9047	10	2726.85	80.4767
11	2364.3	84.9412	12	1744.3	60.1224	13	1590.02	15.6536	14	1463.71	89.0231	15	1385.6	66.8355
16	1349.93	53.0887	17	1283.15	93.5242	18	1111.76	84.8134	19	1072.23	83.6771	20	1032.69	65.8691
21	920.843	96.7146	22	889.023	87.6539	23	835.99	83.1454	24	749.209	66.0315	25	698.105	78.5242
26	600.717	76.0199	27	559.255	72.6303	28	451.261	75.0984	29	411.728	77.9516			

FIGURE NO. 21: IR SPECTRA OF FORMULATION F10 (DRUG + EXCIPIENT)



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	10/24/2008 3:26PM	Update	10/30/2008 0:02PM
Operator	C.Geetha		
File Name	F10		
Sample Name	F10		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3924.43	88.4936	2	3817.4	90.0671	3	3359.39	22.7236	4	2362.37	89.9164	5	1745.26	66.4666
6	1591.95	23.5441	7	1467.56	92.4609	8	1378.85	71.9272	9	1349.93	56.4023	10	1287.97	94.3537
11	1205.29	92.0646	12	1107.9	86.8904	13	1033.66	71.7043	14	998.666	94.584	15	840.812	90.805
16	773.315	82.6483	17	748.245	79.8031	18	618.074	90.5688	19	493.688	86.4193	20	444.512	93.3677

RESULTS AND DISCUSSION

An attempt was made to develop immediate release tablets of Etodolac to increase the rate of dissolution by using intragranular, extragranular and partly intra and extragranular method of addition of crospovidone, sodium starch glycolate as superdisintegrants.

Nine batches (F2-F10) of Etodolac immediate tablets were prepared with crospovidone, sodium starch glycolate at three different concentrations (2%, 4% and 6%) by wet granulation method. The same way one control batch (F1) is prepared without addition of superdisintegrants. Lactose monohydrate, colloidal silicon dioxide PVP, MCC, magnesium stearate, and polysorbate 80 are used as excipients for the above formulations.

COMPATIBILITY STUDIES

The compatibility between the drug and excipients were evaluated by using TLC and IR matching approach.

THIN LAYER CHROMATOGRAPHY

In TLC studies, Etodolac dispersed in various excipients showed the same Rf value as pure compound and no additional spots were detected. TLC studies thus indicated no interaction between Etodolac and excipients in the immediate release tablets formulated. This observation also indicated that Etodolac was not decomposed during the formulation of immediate release tablets.

FT-IR SPECTRAL ANALYSIS

In IR studies, there was no appearance or disappearance of characteristics peaks in pure drug and drug excipient mixture. In Etodolac

IR spectrum, principal peaks at wave numbers were noticed at 1746, 1412, 1034, 748 cm^{-1} (KBr pellet). The IR spectra obtained are given in figure no. 18-21.

This two methods (TLC and IR) conformed that the absence of any chemical interaction between drug and excipients.

FLOW PROPERTIES

Powder blend of drug and excipients were prepared and evaluated for pre-compressional parameters such as angle of repose, bulk density, tapped density, percentage compressibility index and Hausner's compressibility ratio (table no. 32) all for formulation (F_1-F_{10}) were found to be excellent in their flow property. The flow property of pure drug was very poor.

EVALUATION OF ETODOLAC FORMULATED TABLETS

All the formulated Etodolac immediate release tablets (F1-F10) were fulfilled official requirements for weight variation and drug content uniformity (table no. 34). All the tablets prepared were found to contain the medicament within 100±7.5% of labeled claim (table no. 34) Hardness of the tablets in all the batches were found to be in the range of 4.3 to 5.6 kg/m^2 (table no. 34) and was satisfactory. The percentage weight loss in the friability test was found to be less than 1% in all formulations (table no. 34) were found to be good quality fulfilling the official requirements of compressed tablets. And the appearance, thickness, diameter (table no. 33) was found to be good quality fulfilling the general requirements of compressed tablets.

All the formulated Etodolac immediate release tablets containing crospovidone, sodium starch glycolate were disintegrated within 15 min, fulfilling official requirements for compressed tablets, (table no. 34) where

as the disintegrating time of control tablet (F1) was more when compared with Etodolac formulated IR tablets (F2-F10).

The order of disintegration was found to be

F10 > F9 > F8 > F7 > F6 > F5 > F4 > F3 > F2 > F1.

The formulation containing partly intra and extragranular method of addition of disintegrants (F8, F9 and F10) shows faster disintegration than the intragranular (F2, F3 and F4) and extragranular (F5, F6 and F7) formulation.

The faster disintegration of F8-F10 formulation containing sodium starch glycolate and crospovidone by partly intra and extragranular addition method may be due to immediate disruption of tablet into previously compressed granules by the extragranular while the sodium starch glycolate and crospovidone, disintegrating agents within the granules (intragranular) producers further erosion of the granules to the original powder particles. Therefore the two step method (partly intra and extragranular) usually produce better and more complete disintegration than the other two method of addition of disintegrants.

DISSOLUTION STUDIES

The percentage drug released at different time periods (5, 10, 15, 30 and 45 min) from Etodolac immediate release tablets in pH 6.8 phosphate buffer is shown in table no. 35 to 41 and figure no. 8 to 14. The percentage of drug release in F1 formulation was found to be 18.6%, whereas the percentage of drug release in F2, F3 and F4 formulation was found to be 74.8%, 77.5% and 80.1%. Where as the percentage of drug release in F5, F6 and F7 formulation was found to be 70.0%, 75.91% and 77.95% and the percentage of drug release in F8, F9 and F10 formulation was found to be 92.6%, 96.1% and 100.8%.

The t_{50} and t_{90} of all the formulation is shown in the table no. 42 Among the batches formulated, formulation F10 released 90% of the drug

within 8.5 mins and 50% of the drug in 2.3 min; hence it was selected as a best formulation among all nine formulations for immediate release preparation.

Among the tablets formulated F10 formulation release 78.9% of drug release, where as in case of control F1 and marketed sample MS the drug release was 12.3% and 21.6% only.

STABILITY STUDIES

The stability studies were carried out on formulation 10 according to ICH guidelines. At real time and accelerated storage condition there was slight change in the hardness, friability, disintegration time and release characteristics which were acceptable.

CONCLUSION

- ✓ Attempts were made to increase the rate of drug release (disintegration) to enhance the in vitro dissolution of the poorly soluble drug Etodolac by using extra, intra and partly intra and extra granular method of addition of sodium starch glycolate and crospovidone as superdisintegrants and to develop a stable immediate release formulation by wet granulation method.
- ✓ Chemical incompatibilities study confirmed that there is no interaction between drug and excipients need in the formulation.
- ✓ The flow properties of the powdered blend for all the formulation (F2-F10) were found to be excellent.
- ✓ The weight variation, drug content uniformity, hardness, friability, thickness, and diameter of all the formulated tablets were within the specified requirements. The disintegration time for the formulated tablets was less than the control tablets (F1) and market samples (MS) were within the specified limits.
- ✓ *In vitro* dissolution study showed that the formulation F10 shows higher percentage of drug release when compared to control tablet and market sample with respect to t_{50} to t_{90}. The improvement in the dissolution may be due to increase in the rate of drug release (disintegration) by sodium starch glycolate and crospovidone as superdisintegrants by partly intra and extra granular addition method.
- ✓ Hence, the Etodolac can be formulated as immediate release tablets for better pain management.
- ✓ Further work was carried out for *in vivo* studies.

BIBLIOGRAPHY

1. Dion R Brocks and Fakhreddin Jamali. Etodolac Clinical Pharmacokinetics. Clin. Pharmacokinet. 1994, 26(4): 259-274.
2. Ketan P. Shah; Kavita Gumbhir. Shah and Harry G Brittain ETODOLAC. Analytical profiles of drug substances and Excipients – 2002, volume 29, pp 105-140.
3. Shiro Koizuka Shigeru Saito, Hideaki Obata, Masayuki Sasaki, Koichi Nishikawa, Kenichiro Takahashi, Yuji Saito and Fumio Goto. Oral Etodolac, a COX-2 inhibitor, reduces postoperative pain immediately after fast-track cardiac surgery. Journal of Anesthesia. 2004, 18: 9-13.
4. Kichiro Inoue*; Hiroshi Fujisawa; Asahiko Motonaga; Yoshie Inoue; Takashi Kyoi; Fusao Ueda and Kiyosha Kimura – Anti-inflammatory effects of Etodolac – Comparison with other Non-steroidal Anti-inflammatory drugs, J. Biol. Pharm. Bull., 1994, 17(12), 1577-1583.
5. Leon Lachman, Herbert A. Lieberman, Joseph K. Kaning. Pharmaceutical Dosage forms-Tablets, Disintegrating in Tabletting, 3rd Edition, pp 217.
6. Leon Lachman, Herbert A. Lieberman, Joseph K. Kaning. The Theory and Practice of Industrial Pharmacy, Third Edition, pp 331 & 176.
7. www.pharmapedia.com/Tablet: 'The Ruling Dosage form since years'.
8. www.pharmainfo.net/Tablet.
9. United States Pharmacopoeia USP 27/National formulary 22, 2004, United States Pharmacopeias Convention, Inc, Twin rook Park way, Rockville, MD, 2271-2272.

10. United States Pharmacopoeia second edition supplement to USP 26/National formulary 21, 2003, pp 3601-3602.
11. Lusina M.C., Stability Indric T, Tomaic Peko M., Pozaic. L, Musulin. N., Study of Losartan Hydrochlorothiazide tablets. Indian J. Pharm. Sci, 2005, 67(4), 427-431.
12. Ahuja S, Scypinski S, Handbook of modern pharmaceutical Analysis, Academic presim a Harcourt Sciences and Technology Company, San Diego, San Francisco, New York, Boston, London, Sydney, Tokyo, Volume 3, pp 445-483.
13. Tripathi K.D. Essentials of medical pharmacology, 5th Edition.
14. K.D. Rainsford, Anti-inflammatory Drugs in the 21st century, Biomedical Research centre, Sheffield Hallam University, Howard Street, Sheffield, SIIWB, UK, 2007, 3-27, Springer.
15. Stephen L. Curry, DVM; Stephen M. Cogar; James L. Cook, DVM, PhD., Diplomate ACVS. Non-steroidal Anti-inflammatory Drugs: A Review Journey of the American Animal Hospital Association, 2005; 41: 298-309.
16. Martindale-Complete Drug Reference - Monographs, The Pharmaceutical Press. 1982-2008.
17. www.drugindex.com-“Etodolac”
18. Leslie G. Humber, Etodolac: The chemistry, Pharmacology, Metabolic Disposition, and Clinical profile of a novel Anti-inflammatory Pyrano-carboxylic acid, Medical Research Reviews, Ayerst Laboratories, Inc., New York, 1987 vol. 7, no. 1, pp.1-28
19. Jing-min SHI, Shun-guo LAI, Chang-jiang XU, Geng- Li DUAN, Duan LI, Pharmacokinetics difference between S-(+)- and R-(-)-Etodolac in rats. Acta Pharmacological Sinica, August 2004: 25(8): 996-999.

20. Hidetaka Tsumura, Isamu Tamura, Hiroshi Tanaka, Ryo Chinzei, Tsukasa Ishida, Atsuhiro Masuda, Hideyuki Shiomi, Yashinori Morita, Masaru Yosida, Hiromu Kutsumi, Hideto Inokuchi, Minoru, Doita, Masahiro Kurosaka and Takeshi Azuma- Prescription of Non-Steroidal Anti-inflammatory Drugs and co-prescribed Drugs for Mucosal Protection: Analysis of the present status on Questionnaires obtained from Orthopedists in Japan, www. Internal Medicine.com, April 1, 2007.
21. Raymond Crowl, Paul J Sheskey and Paul J Weller. Hand Book of pharmaceutical Excipients, 4th edition 2003.
22. Kamp, H.V., Bolhuis, G.K., Lerk, C.F., Improvement by superdisintegrants of the properties of tablets containing lactose, prepared by wet granulation. Pharm Weekb Sci., 1983, 5(4), 165-171.
23. Solom I.L; Jacob G; Jallad N; Perdomo CA; Mullane J F; Weidler D. Gastro intestinal micro bleeding associated with the use of Etodolac, Ibuprofen, Indomethacin and Naproxen in normal males. J. of Clinical Pharmacology, 1984, 24 (5-6). 240-246.
24. Gaston G W; Mallow R D; Frank J E. Comparison of Etodolac, Aspirin and Placebo for pain after oral surgery. J. of Pharmacotherapy, 1986, 6(5), 199-205.
25. Gordon M.S.; Chowhan Z.T. Effect of tablet solubility and hygroscopicity on disintegrant efficacy in direct compression tablet in terms of dissolution. J. Pharm. Sci. 1987, 76(12), 907-909.
26. Kraml M; Hicks D. R; McKean M; Panagides J; Furst J. The Pharmacokinetics of Etodolac in Serum and Synovial fluid of patients with Arthritis. Clinical Pharmacology & Therapeutics, 1988, 43(5), 571-576.

27. Sangalli M. E; Giunchedi P; Colombo P; Conte U; Gazzaninga A; Manna L. A. Crosslinked Sodium carboxymethyl cellulose as a carrier for dissolution rate improvement of drugs. Bull Chem Pharm, 1989, 128 (7-8), 242-247.
28. N. Zvaifler. A review of the Antiarthritic efficacy and safety of Etodolac. J. of Clinical Rheumatology, 1989, 8, Suppl. N1, 43-53.
29. Brater D.C. Evaluation of Etodolac in subjects with renal impairment. European Journal of Rheumatology and inflammation. 1990, 10 (1), 44-55.
30. Gordon M.S, Chatterjee, B; Chowhan Z.T. Effect of the mode of croscarmelose sodium incorporated on tablet dissolution and friability. J. Pharm Sci, 1990, 79 (1), 43-47.
31. Johnson, J.R; Wang L.H; Gordon M.S; Chowhan Z.T. Effect of formulation solubility and hygroscopicity on disintegrant efficiency in tablets prepared by wet granulation, in terms of dissolution. J. Pharm Sci, 1991, 80 (5), 467-471.
32. Rudraraju V.S; Gordon M.S; Dani K; Chowhan Z.T. Effect of the mode of superdisintegrant incorporation on dissolution in wet granulated tablets. J. Pharm Sci, 1983, 82 (2), 220-226.
33. Ahmed I; Shaikh R.H. Effect of temperature and humidity on hardness and friability of packaged Paracetamol tablets formulations. Pak J. Pharm Sci. 1994, 7 (2), 69-78.
34. Li J.Z; Rekhi G.S; Augsburger L.L; Shangraw R.F. The role of intra and extra granular microcrystalline cellulose in tablet dissolution. Pharm Dev Technol, 1996, 1 (4), 343-355.
35. Rekhi G.S; Eddington N.D; Fossler M.J; Schwartz P; Lesko L.S; Augsburger L.L. Evaluation of in vitro release rate and in vivo absorption characteristics of four metroprolol tartrate immediate-release tablet formulation. Pharm Dev Technol, 1997, 2 (1), 11-24.

36. Chen, C.R; Cho S.L; Lin C.K; Lin Y.H; Chaing S.T; Wu H.L. Dissolution difference between acidic and natural media of acetaminophen tablets containing a super disintegrant and a soluble excipient. Chem Pharm Bull (Tokyo), 1998, 46 (3), 478-481.
37. Richard A. Jones. Etodolac: an overview of a selective COX–2 inhibitor. Inflammo Pharmacology, 18 August 1999, Volume 7, No. 3, pp 269-275.
38. Lopez Solis J; Robles V.L. Effect of disintegrants with different hygroscopicity on dissolution of Norfloxacin / Pharmatose DCL 11 tablets. Int J Pharm., 2001, 216 (1-2), 127-135.
39. L.H. Reddy, Bijaya Ghosh and Rajneesh. Fast dissolving drug delivery systems: A review of the literature, Indian J. Pharm. Sci., 2002, 64 (4): 331-336.
40. Shenoy V; Agarwal S; Pandey S. Optimizing sodium by rapidly disintegrating agents. Indian J. Pharm. Sci, 2003, 65 (2), 197-201.
41. Nayak S.M, and Gopalkumar P. Design and optimization of fast dissolving tablets for promethazine theoclate. Indian Drugs 2004, 41 (9): 554-556.
42. Stephen L. Curry, DVM; Steven M. Cogar, James L. Cook, DVM, PhD, Diplomate ACVS. Non-Steroidal anti-inflammatory drugs: A review. J. Am Animal Hosp Assoc. 2005; 41:298-309.
43. Souliman S, Blanquet S, Beyssac E, Cardot JM. A level of *in vitro / in vivo* correlation in fasted and fed states using different methods: applied to solid immediate release oral dosage form. Eur J Pharm Sci. 2006 Jan; 27(1):72-9.
44. Manzo RH, Olivera ME, Amidon GL, Shah VP, Dressman JB, Barends DM. Biowaiver monographs for immediate release solid oral dosage forms: amitriptyline hydrochloride. J Pharm Sci. 2006 May; 95(5):966-73.

45. Dukić-Ott A, Remon JP, Foreman P, Vervaet C. Immediate release of poorly soluble drugs from starch-based pellets prepared via extrusion/spheronisation. Eur J Pharm Biopharm. 2007 Nov; 67(3):715-24.
46. El-Barghouthi M, Eftaiha A, Rashid I, Al-Remawi M, Badwan A. A novel superdisintegrating agent made from physically modified chitosan with silicon dioxide. Drug Dev Ind Pharm. 2008 Apr; 34(4): 373-83.
47. Sekar V, Chellan VR. Immediate release tablets of telmisartan using superdisintegrant - formulation, evaluation and stability studies. Chem Pharm Bull (Tokyo). 2008 Apr; 56 (4):575-7.
48. European Pharmacopoeia, 2005, volume-2, pp 1560.
49. Ayman A; and Wafaa S. Hassan, Spectrophotometric determination of Etodolac in pure and pharmaceutical formulations, Chemistry Central Journal, April 2008, 2:7.
50. N.M. El Kousy, Spectrophotometric and spectrofluorimetric determination of Etodolac and Aceclofenac. Journal of Pharmaceutical & Biomedical Analysis. 1999, vol. 20, 185-194.
51. Hyun-soolee, Il-Mokang, Heon-woolee, Ji-Hyung Seo,,Ju-Hee Ryu, Sang- Jun Choi, Myung-Jae-Lee, Seo-Young Jeong, Young-Wuk Cho, Kyung-Tae Lee. Development and validation of high performance liquid chromatography-Tandem mass spectrometry for the determination of Etodolac in human plasma. Journal of Chromatography B, 2008, 863, 158-162.
52. Indian Pharmacopoeia 1996 volume. I, A-144-169.